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Vol 63 No 5 May 1988

ARCHIVES OF DISEASE IN CHILDHOOD

CWK-404690-12-P024930

The Journal of the British Paediatric Association

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BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

ISSN 0003-9888 ASTM CODEN ADCHAK 63(5), 465-578, (1988)

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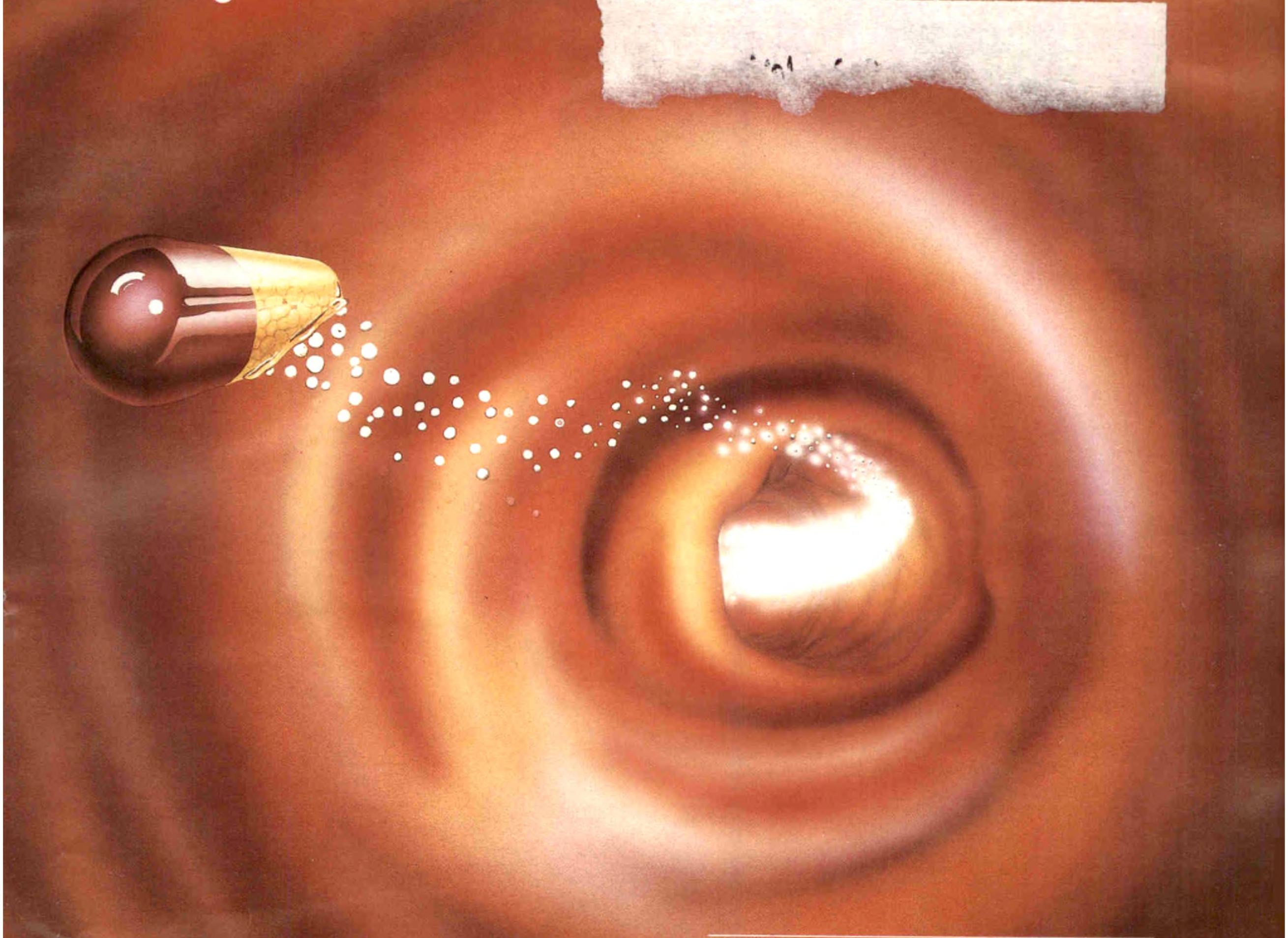

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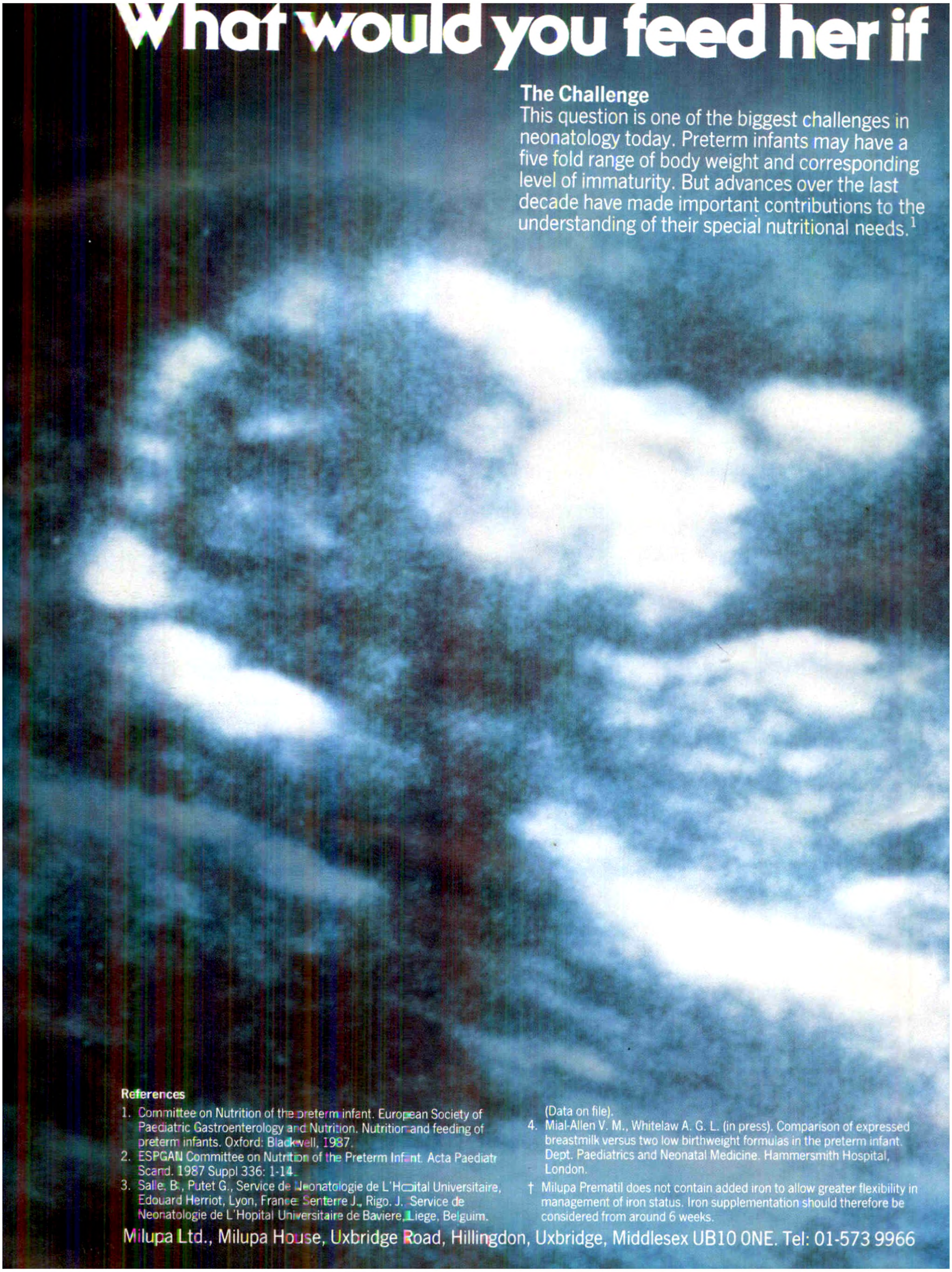

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2. ESPGAN Committee on Nutrition of the Preterm Infant. Acta Paediatr Scand. 1987 Suppl 336: 1-14.
3. Salle. B., Putet G., Service de Neonatologie de L'Hopital Universitaire, Edouard Herriot, Lyon, France. Senterre J., Rigo. J. Service de Neonatologie de L'Hopital Universitaire de Baviere, Liege, Belguim. (Data on file).
4. Mial-Allen V. M., Whitelaw A. G. L. (in press). Comparison of expressed breastmilk versus two low birthweight formulas in the preterm infant. Dept. Paediatrics and Neonatal Medicine. Hammersmith Hospital, London.

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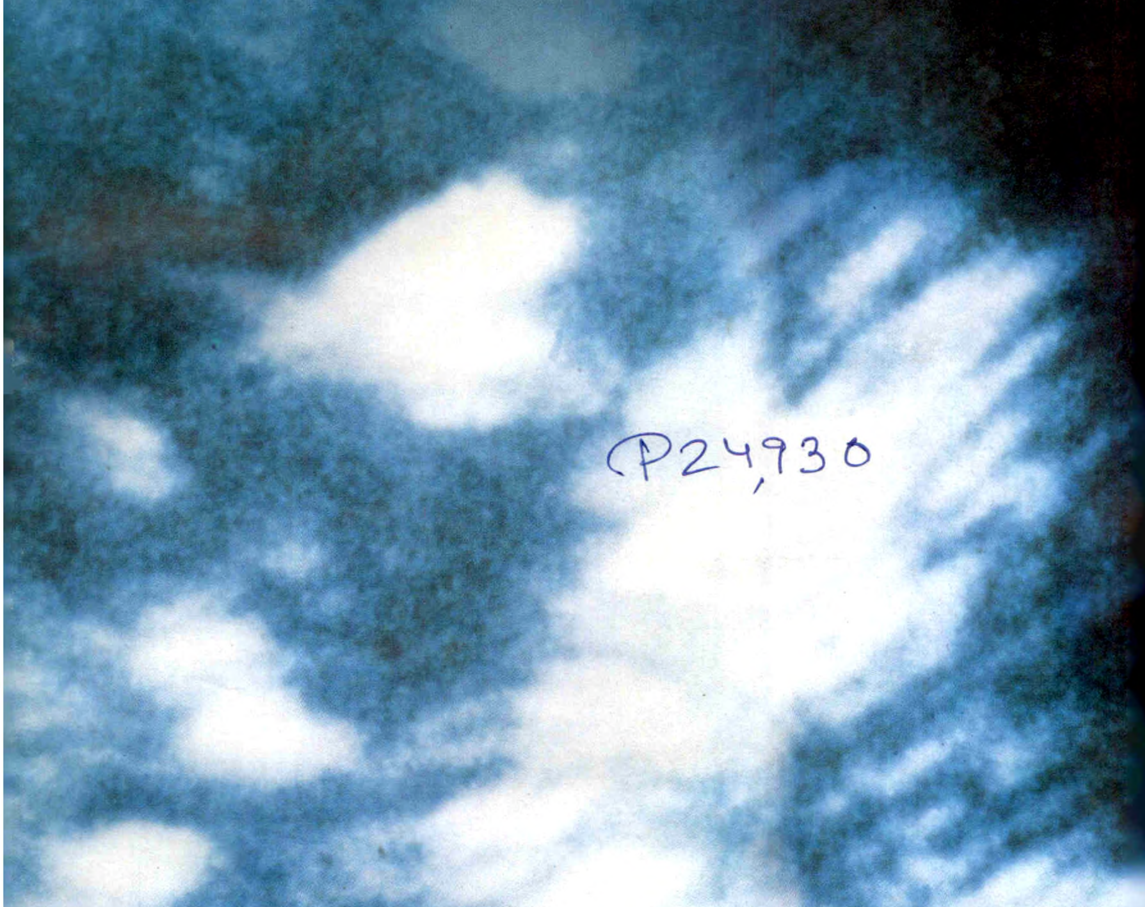

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Annotations

Auditory brainstem response in paediatric audiology

The functioning of the auditory system has been extensively investigated in both man and animals using recordings of electrical activity evoked by sounds. Early investigators encountered the problem of detecting the response to a sound stimulus when the background electrical noise was high. The introduction of signal averaging and the subsequent development of the digital averaging computer, however, completely revolutionised the field of electric response audiometry and it is now possible to measure electrical responses to sound from the entire length of the auditory pathway.[1]

Auditory evoked potentials are often described as early, middle, or late latency responses according to the time at which the response occurs after the auditory stimulus. Each class represents electrical activity from a progressively higher level of the auditory pathway. The electrical activity originating in the auditory nerve and brainstem pathways is known collectively as the auditory brainstem response. They form part of the early latency responses and arise in the first 10 milliseconds after an auditory stimulus. The first definitive description of the auditory brainstem response in humans was given by Jewett and Williston in 1971,[2] although Sohmer and Feinmesser first recorded these neurogenic responses in 1967.[3] Jewett showed that the response evoked by a high intensity click stimulus, and recorded from a vertex and ipsilateral mastoid electrode configuration, consists of a series of up to seven waves (designated I to VII in the Jewett classification as shown in fig 1). These waves are a far field recording of the electrical activity from sequentially activated neurones of the ascending auditory nerve and brainstem pathways.

The precise origins of these waves are not well understood and are complicated by the interaction between the possible generator sites. The proposed origins are based largely on either studies in animals,[4] patients with brainstem disorders,[5] or more recent comparative studies of surface and depth recorded auditory brainstem responses in patients undergoing surgery.[6 7] Wave I is known to be the compound auditory nerve action potential and is similar to the action potential recorded in electrocochleography.[8] Wave II is now thought to arise predominantly from proximal regions of the auditory nerve and wave III from the cochlear nucleus. The superior olivary complex is considered to be the main source of wave IV and the lateral lemniscus wave V. Waves VI and VII are thought to arise mainly from the inferior colliculus.

As well as these fast individual waves of the auditory brainstem response, as described by Jewett and Williston, there are also slow waves associated with the response which consist of a peak at roughly the same latency as wave V and a trough at a latency of about 10 milliseconds as shown in fig 1. This trough is termed a slow negative component at 10 milliseconds (SN10) by Davis and Hirsh[9] and is thought to originate in the midbrain probably representing postsynaptic activity within the inferior colliculus.[6]

The auditory brainstem response is considered by most workers to be the best choice of all the auditory evoked potentials for objective assessment of hearing acuity in young patients.[10–12] Although the audiological information provided by the auditory brainstem response is limited in some situations, the slow wave V and SN10 components can be recorded reliably with stimulus intensities close to the threshold of hearing, as shown in fig 2, and these components are resilient to the effects of habituation and sleep.

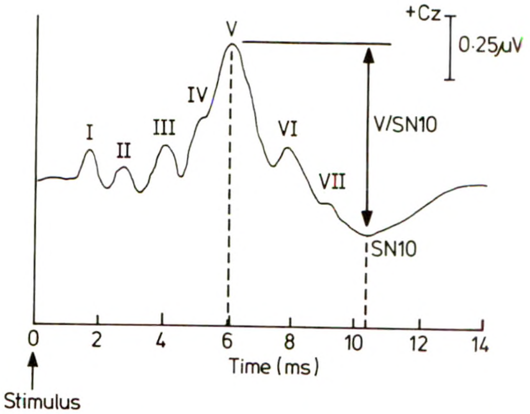

Fig 1 *The typical configuration of the auditory brainstem response.*

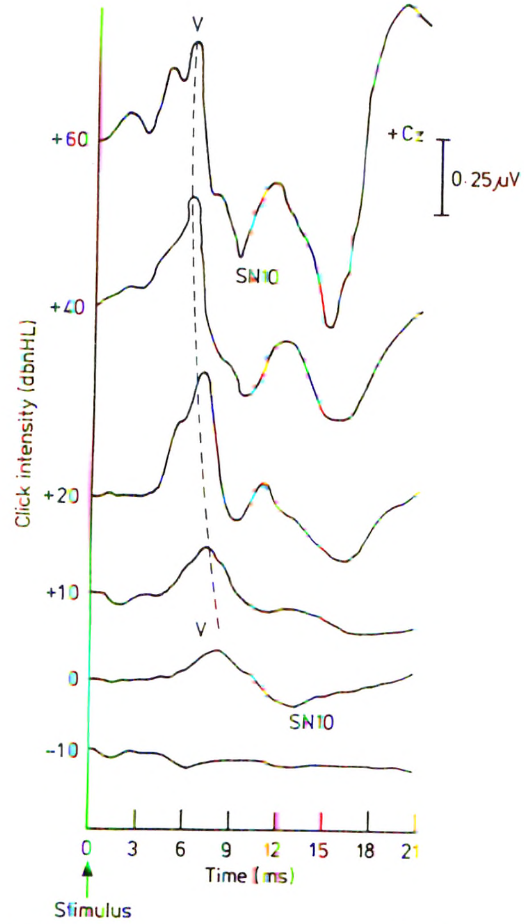

Fig 2 *Auditory brainstem responses recorded in a normally hearing subject.*

Recording the auditory brainstem response

The auditory brainstem response is measured from the differential signal across a pair of surface recording electroencephalography electrodes. One electrode is positioned over an area of high response activity (active) and a second electrode over an area of low response activity (reference). The optimum stimulus to evoke the response must be fairly abrupt so as to produce a good degree of synchrony of firing of the nerve fibres, and for this reason a click is widely used. This is generated by passing a 100 microsecond electrical pulse through a headphone and is usually calibrated in decibels above the hearing threshold of normally hearing subjects (dbnHL). The resultant acoustic stimulus has energy over a wide range of frequencies, and this results in an auditory brainstem response which is generated mainly by the basal (high frequency) turn of the cochlea. The click auditory brainstem response threshold corresponds reasonably well with the average subjective hearing thresholds across the frequency range from 2 kHz up to 4 kHz.[13]

The auditory brainstem response is very small compared with the background electrical noise and a repetitive stimulus is required so that the response-to-noise amplitude ratio can be improved using signal averaging. It is usually necessary to average about 2000 or 4000 individual sweeps in order to achieve reliable identification of the response waveform, the precise number being dependent on the recording conditions. The wave V and SN10 components are fairly resilient to fast rates of stimulation and a stimulus rate of 20 to 30 Hz can be employed without risk of adapting the response. In audiological investigations, recordings are made at different levels of stimulus intensity until a response is no longer observed and this is taken as an estimation of the hearing threshold. The stimulus intensity is usually changed in steps of 10 db close-to-threshold rather than 5 db (because of time constraints) and the threshold is estimated to the nearest 5 db using interpolation. Usually, in routine investigations, the test does not continue below a stimulus level of 20 db above the threshold of normal hearing.

The merits and limitations of tests for auditory brainstem response

The auditory brainstem response is a valuable audiological test for the very young or the otherwise difficult to test child. It does not, however, offer a panacea to replace conventional testing and children should only be referred for electric response audiometry when conventional tests have failed to provide reliable or adequate results. From a well documented paediatric audiology service with an open access referral system it has been found that electric response audiometry support is needed only in approximately 3% of the total caseload.[14] The auditory brainstem response is particularly valuable in the important first few weeks of life when behavioural observation testing can be difficult to carry out.

In recent years equipment costs and the ease and convenience of equipment use have made the auditory brainstem response technique more accessible to inexperienced or non-scientific personnel, and it is therefore very important to consider the following factors before applying the technique in a routine audiological service.

(1) The procedure can be time consuming.

(2) The environment in which the test is

performed must be free from high levels of acoustic and electrical interference.

(3) Sedation or anaesthesia may be needed for young children in order to achieve satisfactory recording conditions.

(4) Skill in interpretation of the auditory brainstem response waveforms is required.

The auditory brainstem response can be a time consuming procedure particularly when recording conditions are not ideal. Most young babies (below 6 months) will settle and sleep sufficiently to allow the test to be carried out satisfactorily without any sedation. The difficult age group is between one to three years and some of these children will need sedating. Only in exceptional circumstances should it be necessary to resort to the use of anaesthetics.

Interpretation of the auditory brainstem response waveforms requires a high level of expertise and experience and it may be quite difficult to recognise a genuine response among the background noise, particularly when the recording conditions are not ideal. This situation can easily lead to a misinterpretation of the hearing threshold. The click evoked response also provides limited audiological information compared with conventional tests because although clicks give a reasonable measure of high frequency response they do not provide information about the hearing at low frequencies. A low frequency conductive hearing loss would not be identified with click stimuli and, conversely, results from a patient with a steeply sloping high frequency loss could be misinterpreted to show a much more severe hearing impairment than in fact exists. The use of tone pips at lower frequencies than the click, down to about 1 kHz, can provide some indication of hearing thresholds in the mid to low speech frequency region and will help to differentiate between these cases of low and high frequency hearing impairment.[15] [16] Good recording conditions are required for reliable identification of the tone pip auditory brainstem response as the response waveform is not as clearly defined as for the click response.

Another limitation of the test for auditory brainstem response is that unlike subjective audiometry, including speech tests of hearing, it does not sample the entire auditory pathway and hearing disorders of central origin cannot be investigated.

If hearing aids are recommended, initially on the basis of electric response audiometry measurements, follow up testing by conventional means should always be carried out wherever possible both before and after the provision of hearing aids. The conventional tests are needed to provide a more comprehensive audiological picture including measures of sound tolerance, aided and unaided threshold comparisons, acoustic dynamic range, and, where possible, speech audiometry.

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Archives of Disease in Childhood, 1988, **63**, 468–470

Malaria vaccines

At a conservative estimate there are about 100 million cases of malaria in the world each year.[1] Recent community based studies in West Africa give credence to the oft quoted, but previously poorly substantiated, estimate of a million childhood deaths a year in sub-saharan Africa alone.[2] Malaria, particularly *Plasmodium falciparum*, remains a major killer of the world's children. The postwar successes in eradicating malaria from a number of temperate and subtropical areas reached a limit set not only by logistic problems, escalating costs, and growing insecticide resistance but also by natural epidemiological factors. Malaria could never have been eradicated from its heartland in tropical Africa, even with the optimum use of the measures available at that time. The present situation is not even stable. The combination of rapidly emerging multidrug resistance, social and political dislocation in some countries, and unplanned urbanisation in others is a cause for real worry. New approaches are needed to bolster currently available control measures and an antimalarial vaccine has become the holy grail of malaria research.

What kind of malaria vaccine?

Currently most effort is being directed at developing vaccines against three separate stages of the parasite's life cycle.

(1) The sporozoite—an effective vaccine would prevent entry of the infective stage into the liver and thus block subsequent development.

(2) The blood stage—in this case sporozoites would enter the liver and develop normally but an effective vaccine would prevent the subsequent rapid expansion of blood stages and thus limit clinical illness.

(3) The sexual stage—an effective vaccine would not protect the recipient against illness but would render the sexual forms of the parasite, which appear during the later stages of a blood infection, unable to infect mosquitoes. Such an 'altruistic' vaccine would be transmission blocking and would be used as an adjunct to other control measures in specific epidemiological settings.

The ideal vaccine would, of course, be cheap, completely safe, and totally effective! What constitutes a useful vaccine, however, will depend on the specific requirements of the group being vaccinated. This annotation is mostly concerned with children in Africa, who stand in greatest need and also present the most difficult challenge. For this group a vaccine will certainly need to be cheap and safe but it will also have to give longlasting protection against clinical disease and be available in formulations capable of being used in existing vaccination schedules. In other areas of the tropics, particularly parts of South East Asia, the balance between malaria and current control measures is such that a vaccine conferring little clinical protection but giving good transmission blocking immunity may be enough to tip the balance against the parasite. Finally there is a large group of non-immune expatriates who visit endemic areas for short or medium terms. For this group risk benefit analysis is important, as a vaccine which gives even short term protection to only some recipients may have uses if it is safe. The attractiveness of such an adjunct to available measures might increase as the effectiveness of available prophylactic drugs decreases.

Rationale for a human malarial vaccine

What are the grounds for believing that vaccination is an achievable aim? Firstly, people do become immune to clinical malaria—the emergence of stable societies in Africa would not have been possible if that were not the case. In highly endemic areas children suffer the brunt of morbidity and mortality; adults become functionally immune to symptomatic disease but not to low level parasitisation. Secondly, it is clear from many animal models that vaccination with whole parasites can produce varying degrees of immunity. An important point to emerge from such studies is that immunity is both species and stage specific—that is, successful vaccination with sporozoites will protect against sporozoite challenge but not against the direct innoculation of blood stage parasites and vice versa. These background facts have been clear for many years but the problems of ever obtaining antigenic material from the different parasite stages in either sufficient quantity or of sufficient purity seemed unsurmountable. The arrival on the scene of monoclonal and recombinant DNA technology changed all that.

Progress so far

Most work is orientated towards vaccines against *P* *falciparum* because it is the major killer, but work on vaccines against *P vivax* is also gaining momentum. For all three parasite stages the general strategy is the same; antigenic analysis of the parasite and identification of antigens capable of inducing potentially protective immunological responses, cloning and sequencing the genes for such 'protective' antigens, and then production either by recombinant DNA technology or artificial synthesis of subunit vaccines.

To date most progress has been made with the antisporozoite vaccine. Sporozoites have a surface coat consisting of a single polypeptide, the circumsporozoite protein. Genes for the circumsporozoite protein of a number of malarial species have been cloned. Antibodies capable of blocking the penetration of sporozoites into hepatocytes turn out to be directed towards a region of multiple tandem repeats of short runs of amino acids. The repeat motifs are characteristic for each malarial parasite. Most importantly, in the case of *P falciparum* the simple repeat structure, based on just four amino acids, turns out to be invariant between all strains so far examined. Two experimental vaccines based on the repeat sequence, one synthesised and one produced by recombinant technology, have recently undergone preliminary trials in human volunteers.[3 4] In both trials there was a degree of protection against sporozoite challenge in some vaccine recipients. Responses to vaccination, however, showed wide variation and were poorly sustained and evidence for protection was based mainly on relatively small increases in time to patent parasitaemia from challenge. In each trial one individual was apparently completely protected but the numbers involved are too small to bear further analysis. Some commentators have been disappointed by these results, others have been elated by the success. In reality both responses are appropriate, the failures do show how much remains to be done and some of the problems are discussed below. But this should not detract from the real achievement, the idea that subunit vaccines can under certain circumstances protect against human malaria has been strengthened and this should give encouragement to all working on vaccines against other stages and other protozoan parasites.

The position with regard to blood stage vaccines is more complicated. Many blood stage antigens have now been characterised and in several cases the genes have been cloned. Some antigens turn out to exhibit marked antigenic diversity, making them unsuitable as vaccine candidates. In other cases defining epitopes capable of inducing protection has not been straightforward. However, two blood stage antigens (known by their relative molecular mass) are at an advanced stage of investigation. Pf195 is a quantitatively major glycoprotein on the surface of intracellular erythrocytic schizonts. During red cell rupture and reinvasion the protein undergoes processing to several smaller molecules forming part of the merozoite's surface coat. Immunisation of mice with the analogous protein of a rodent malaria resulted in impressive protection[5] though vaccination of monkeys with affinity purified Pf195[6] or synthetic peptides representing parts of the processed molecule[7] have produced only modest partial protection. The second antigen, Pf155 (also known as RESA—ring infected erythrocyte surface antigen) is released from merozoites during red cell invasion and is incorporated into host red cell membranes. The gene for Pf155 has been cloned and sequenced and initial vaccine trials in monkeys with recombinant proteins corresponding to various regions of the molecule have given encouraging results.[8] It seems likely that human trials of blood stage vaccines based on one or both of these molecules will begin within the next year or two. Antigametocyte vaccines have tended to be less 'news worthy' probably because they do not offer the possibility of individual protection. Nevertheless recent progress has been rapid and several candidate antigens have been identified.

The remaining problems

The main technical problems still to be overcome, well illustrated by the antisporozoite vaccine, are how to induce strong, longlasting responses in all vaccinees. There are two vital areas, firstly the development of acceptable and effective adjuvants and secondly the definition of epitopes capable of inducing T helper responses. The next generation of experimental antisporozoite vaccines will probably incorporate sequences representing such epitopes from within the circumsporozoite protein. There is a lurking fear here, that it would be ironic if natural T cell epitopes turned out to lie in regions of the molecule capable of exhibiting the greatest diversity. Putting these worries aside, the optimistic view is that it will prove possible to arrive at effective synthetic vaccines, probably incorporating several different antigens. We will then be faced with the problems of testing candidate vaccines. Why should this be problematic? Two aspects can be illustrated; firstly malarial epidemiology has been traditionally based on the use of cross sectional malariometric indices such as parasite rates and spleen rates. These have been used to generate models centred on the parasitisation of communities. The primary aim of vaccination, however, will not be to eradicate parasitisation per se but to limit morbidity and mortality. The factors governing the relation between parasitisation and disease are not understood. What is clear is that traditional malariometric tools will not be adequate for monitoring vaccine trials. The only acceptable end point of a vaccine trial is a reduction in deaths and severe disease and this will necessitate very large trials. This is not a fundamental problem, epidemiologists are used to the idea of big trials but it does mean that a whole new set of epidemiological tools will have to be developed for detecting and measuring malaria specific morbidity and mortality under difficult field conditions. A second problem arises from the fact that an essential part of any large scale trial will be monitoring the effect of an intervention on the one thing which does already protect people from malaria, the development of natural immunity. Unfortunately work on naturally acquired immunity to malaria has lagged behind the more basic aspects of malarial research with the result that we simply do not yet know how to measure immunity to malaria. It is clear that new initiatives to stimulate malarial field research will be required before the anticipated fruits of the last decade's advances can be realised. Finally, it has to be noted that many children continue to die from diseases for which good preventative measures already exist. The successful field testing of a malarial vaccine would in many ways mark the beginning of the most difficult part of the story.

Conclusions

Developments to date give rise to cautious optimism. Considerable problems remain but they can probably be overcome. So how far away are we from having a useful vaccine? The answer to this question depends to some extent on what you want one for. It is not inconceivable that vaccines suitable for use as adjuncts to other prophylactic measures in subjects with limited exposure will be available over a five to ten year time span. But for children in the tropics and particularly in sub-saharan Africa it is not likely that malarial vaccines will have any perceptable impact before the end of the century. By that time another 10 to 20 million children will have died of malaria. A malaria vaccine is not just around the corner for them, but it has probably moved to the right side of the horizon.

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Archives of Disease in Childhood, 1988, **63,** 471–472

The future of child benefits in the United Kingdom

The implementation of the 1986 Social Security Act in April 1988 marked an important milestone in the development of financial support for children. Confronted by a substantial body of evidence which showed that poverty is most extreme among families with children,[1 2] the government has chosen to shift the balance of support away from pensioners, single people, and higher income families towards families with children on very low incomes. In the context of social security spending as a whole, the size of the transfer which has been achieved is miniscule. Nevertheless, the move was a bold one in political terms as pensioners have long been regarded as one of the natural constituencies of the Tory party, while the history of child benefit is littered with political casualties.[3]

The aims of reform

The 1986 Act followed a series of ministerial reviews, a green and a white paper. The government's intention in reviewing social security provisions was to arrive at a system that was: (a) capable of meeting *genuine* need; (b) consistent with its economic objectives; and (c) simpler to understand and easier to administer.[4] No new money was to be made available.

The government, in its green paper,[5] articulated 'two clear and distinct aims in helping families with the cost of bringing up children': (1) 'to provide help for families generally'; and (2) 'to provide extra help for low-income families.'

A new benefit structure

Child benefit, payable for all children under 16, has been the principal mechanism for providing generalised financial assistance to families since its introduction in 1977. Although the government considered both means testing or taxing child benefit and 'fine tuning' it on particular types of family, all these strategies were rejected on practical grounds rather than for reasons of principle.[5] While child benefit came out of the reviews unscathed (though see below), maternity grant has been made means tested and maternity allowance made taxable.

The most radical changes affected means tested benefits which are designed to provide extra help for low income families. Supplementary benefit, aimed primarily at those not in full time employment, was replaced by a combination of income support and interest free loans (payable under the new social fund) which take the place of the cash grants (single payments) that used to be available to meet exceptional needs. Family income supplement—for working families—was replaced by family credit while housing benefit, available to all low income householders regardless of employment status, was restructured but retains the same name.

Reflecting the aim of simplification and the desire to enhance work incentives, all three schemes share a related means test. A family is entitled to income support (and housing benefit) if their income is less than their requirements. Requirements are calculated as the sum of a personal allowance for the claimant (and his or her partner), an age related allowance for each child and a fixed family premium. The maximum family credit is payable to working families with net incomes at or below the personal allowance for a couple on income support and is progressively reduced for families on higher incomes.

Impact of the reforms

Family credit is more generous than family income supplement used to be and the government expects twice as many families (400 000 in total) to be eligible.[6] At face value children also gain under the new income support and housing benefit schemes, although entitlement to housing benefit stops at much lower income levels than before. Official figures indicate that 71% of two parent families entitled to means tested benefits are made better off as a result of the structural reforms, a fifth of them by over £5 per week, and only 23%—most of them working families facing cuts in their housing benefit—lose out.[7] The picture is very different for other types of claimant. Fifty per cent of young single claimants, 59% of pensioner couples, and 82% of other childless couples stand to lose benefit, although some current claimants are covered by special transitional protection.

Lone parents fared less well than other families, although there is no evidence that their needs are any less, indeed quite the contrary.[8] Only 50% of lone parents claiming benefit gained from the reform while 39%, few of whom had their benefit protected, lost an average of £2·90 per week.

Forebodings

On paper, the reforms mean that in a full year £191 million of means tested benefit will be redirected to families with children and, notably, to traditionally two parent units. The official figures, however, ignore the abolition of single payments, one off lump sum payments made to supplementary benefit claimants in order to meet exceptional needs, and their replacement by loans under the social fund. For most families on income support the loss of single payments will be more than the increase in weekly benefit.[9] [10]

Also, while the structure of child benefit remained intact the government chose not to increase the rate of benefit in line with inflation. This resulted in an annual saving of £120 million. Child benefit (£7·25 per week) now equates with less than half the allowance payable for a 10 year old on income support (including the family premium) and represents less than a third of the direct costs attributable to a child of that age.[11] However, the government gives greater priority to reducing the risk of poverty among families than to making a general contribution to the costs of bringing up children. The deindexing of child benefit had no effect on families in receipt of means tested benefits although it reduced the real incomes of seven million other families with children.

The social security green paper defended child benefit, which it described as 'simple, straightforward [and] well understood.'[5] But, current ministers believe that it is 'ill-targeted' and that it is consequently not meeting genuine need.[12] If child benefit is phased out, or in other ways reduced in value, it will erode still further society's contribution to meeting the very real costs of children, a contribution which in the 1950s was higher than it is today.[13]

In sum, the government has funded improved benefits for the poorest children by taking benefit away from other claimants. Additional moves in tl direction, which seem likely to involve furth reductions in the value of child benefit, will me that the needs of the most deprived will be paid 1 by families who are themselves at the most financia vulnerable stage of the life cycle.[14]

All the official statistics quoted in this annotation are for Gr Britain.

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Archives of Disease in Childhood, 1988, **63**, 473–478

Original articles

Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors

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SUMMARY A questionnaire study regarding airway morbidity in children and environmental factors was performed in April 1985. The parents of 5301 children, aged 6 months to 16 years, from different rural areas in mid Sweden were sent a validated questionnaire and 4990 (94%) responded. The cumulative prevalence of bronchial hyperreactivity was 9·7% and of allergic asthma 5·2%. Children living near a paper pulp plant more often had symptoms suggesting bronchial hyperreactivity (124 (13·0%), relative risk 1·3) and allergic asthma (68 (7·1%), relative risk 1·3). In children living in a damp house problem bronchial hyperreactivity was found in 76 (19·0%) (relative risk 1·9) and allergic asthma in 35 (8·7%) of the children (relative risk 1·9). Children living in a damp house with parents who smoked had the highest figures: bronchial hyperreactivity was found in 44 (23·5%) (relative risk 2·8) and allergic asthma in 22 (11·6%) (relative risk 2·5). The results indicate that various moderate environmental pollutants may act synergistically to increase bronchial hyperreactivity and allergy especially in children with a family history of allergy.

Several studies in recent years have indicated that the occurrence of asthma and allergic disorders may be increasing in industrialised countries.[1–4] The reasons for this are not fully understood, but various environmental pollutants may play a part. For example', exposure of children to tobacco smoke is widespread and has been shown to give increased bronchial hyperreactivity,[5] an increased number of respiratory tract infections,[6] wheezy bronchitis,[7] increased prevalence of atopic disease,[8] and increased serum IgE concentrations.[9] Other air pollutants, which may affect the airways in children, include sulphur dioxide, which irritates mucosal membranes[10] and may also facilitate production of IgE in laboratory animals.[11]

The air indoors may become polluted because of evaporation of chemicals from plastic materials in carpets, furniture, and household equipment. In Scandinavia most houses built after the energy crisis in 1973 have been insulated extremely well in order to minimise heating costs. There is often less than 0·5 air exchanges per hour, which sometimes leads to increased dampness indoors with favourable conditions for mite and mould growth.

The aim of this study was to estimate the importance of some environmental factors in the development of symptoms reflecting bronchial hyperreactivity and allergic conditions of the respiratory tract. (In the same study we also evaluated the incidence of respiratory tract infections.)

Subjects and methods

STUDY AREA

The population was comprised of children living in seven rural areas as defined by the 'zip' code and situated to the north and west of the city of Norrkoping (fig 1). In area 4 there was a pulp and paper plant, but in the other areas there were no

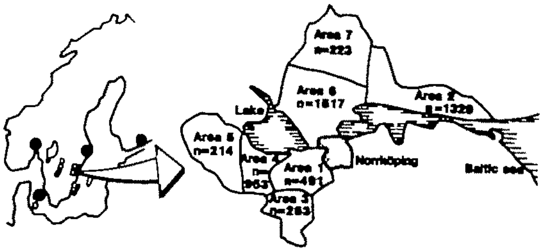

Fig 1 *Map of Sweden and areas included in the study*

polluting industries. Pollution, from remote areas and the European continent in the form of solid particles that could directly influence the respiratory morbidity, has occurred occasionally, but was essentially similar in all the areas. (K Persson, head of the Meteorologic Department of the Swedish Meteorologic and Hydrologic Institute. Personal communication.)

For the purpose of studying the possible effects of general air pollution from industry, the children in areas 2 and 4 were selected for a detailed analysis. Area 2 was the area furthest away from area 4 and the city of Norrkoping, and it was therefore least likely to be influenced by regional pollution. It was situated in a forested region about 150 m above sea level.

Area 4 with the combined paper pulp and paper making plant was situated in an open, flat country at about 5 m above sea level and was traversed by a river, which remained unfrozen during winter because of the process water from the factory. The warming up of the water resulted in some fog in the immediate vicinity of the river during part of the year. Apart from this the differences in climate between the areas were minor. The annual mean temperature was 0·3°C lower in area 2 than in area 4. The rainfall was 570 mm v 540 mm per year in the respective areas.

The pulp and paper plant operated continuously and processed 350 000 tons each year. The daily discharge of pollutants into the surrounding atmosphere was composed of roughly 0·1–1 tons of solids, 0·5 ton of sulphur dioxide, and 0·08 ton of hydrogen sulphide. Mercaptans were always present, causing the typical 'paper pulp plant smell' in the area, but the concentrations were extremely low. In addition, some chloride could have been released in the plant area, but this would have occurred only occasionally and in small quantities. Chlorinated organic material was likely to escape from the process, but no details were known in this respect. The discharge as measured in 1976 was even then below the Swedish health standards, that is, 0·012 ppm for sulphur dioxide and 0·003 ppm for solid particles as mean values for the six winter months.[12] Since 1976 the discharge from the plant has continuously decreased and is now only 5% of the level at that time. At the time of the study, however, there were periods with considerably higher concentrations of sulphur dioxide and the other discharges that lasted for a few hours. These periods occurred at least once every month.

QUESTIONNAIRE

A questionnaire was mailed in April 1985 to the parents of all 5301 children aged 6 months to 16 years who were living in the seven areas. Reminders were mailed after three and six weeks. By this procedure data were obtained from 4990 children (a response rate of 94%).

The questionnaire included 43 questions concerning various environmental factors, socioeconomic data, incidence of respiratory tract infections, symptoms of bronchial hyperreactivity, and allergic disease. The environmental factors included in the questionnaire are summarised in table 1. For stratification in the statistical analyses the type of dwelling was used as a crude indicator of socioeconomic standard. The outcome variables are presented in table 2.

VALIDATION OF THE QUESTIONNAIRE

To validate the questionnaire 100 children were randomly selected from the original sample before the start of the study. Out of these, 95 responded to the questionnaire, and they were offered a physical

Table 1 *Environmental exposure factors*

Residential area
Type of dwelling (one family house or apartment)
Type of house (construction, building material, wall to wall carpets)
Type of heating
Signs indicating damage due to dampness in the house
Furred pets in the house at the time of the study and previously
Parental smoking at the time of the study and previously
Type of infant feeding during the first six months of life
Type of daily care for preschool children

Table 2 *Questions asked regarding hyperreactivity and allergy (Frequency of items was based on the answers to these questions)*

1 Prolonged cough	Does your child usually cough for more than two weeks during an ordinary common cold?
2 Exercise-induced cough	Does your child often cough when exercising (running, playing) or otherwise getting short of breath?
3 'Breathing problem'	Has your child ever had a 'breathing problem' with heavy breathing and wheezing?
4 Allergic asthma	As for 3. Does this occur when in contact with deciduous trees, grass, flowers, or furred animals?
5 Allergic rhinitis	Has your child ever had attacks of sneezing, nasal congestion and/or an itching nose without having a cold? Does this occur when in contact with deciduous trees, grass, flowers, or furred animals?
6 Damage due to dampness	Does your dwelling have any damage caused by dampness?

Figures for items 3, 4, and 5 give the cumulative prevalence, while 1, 2 and 6 give the prevalence examination including a skin prick test and blood sampling. Five of the 95 responders could not be reached a second time; five declined to participate because of fear of test procedures and four had recently been to hospital for confirmed allergic disease and therefore declined.

The remaining 81 children with their parents were interviewed by a paediatrician (SA) and the answers were entered in a second questionnaire, which was identical to the one that had been mailed to the parents. These answers were then compared with the ones given by the subjects in the initial questionnaire.

The skin prick tests were performed with biologically standardised extracts of birch, timothy, and mugwort pollen, house dust mites, cat, horse, and dog epithelium, Cladosporium and Alternaria at a concentration of 100 000 biological units/ml (Pharmacia). Histamine chloride 10 mg/ml was used as a positive control.

Venous blood samples were obtained for analysis of total concentrations of serum IgE and concentrations of specific antibodies The tests were done using Phadebas IgE PRIST and Phadebas RAST (Pharmacia) as recommended by the manufacturer.

A representative sample of 34 houses were visited by health inspectors to evaluate 'damage due to dampness.'

STATISTICAL METHODS

The statistical analyses of the data were based on the Mantel–Haenszel procedure for the calculation of χ^2 values and for the estimation of the overall rate ratios.[13 14] Stratification was found necessary in various respects to account for possible confounding and modification of effect as further indicated in the tables of the result section

The validation study was approved by the Human Research Ethics Committee of the University of Linkoping.

Results

VALIDATION OF THE QUESTIONNAIRE

A 95% concordance was obtained for the questions about bronchial hyperreactivity and asthma between the answers in the interviews and the questionnaires. The questions about the construction material of their houses were, however, difficult to answer for most parents and were therefore excluded from the final analysis of the data For all the other questions used in the questionnaire the specificity was 70% and the sensitivity 90%.

Thorough analysis of the representative selection of 34 houses confirmed that when parents claimed that there was a damage due to dampness in the house, experienced health inspectors agreed. Visible mould growth or a specific smell, or both, were noted by the inspectors in 14 out of 23 'damp' houses *v* only three out of 11 houses where no dampness was suspected. In the nine houses in which dampness was claimed to occur and no confirmation could be obtained, there were indications of dampness in the past—for example, dry damp spots and also reports of an improvement of the drainage system.

Samples of dust and air from the houses were also obtained for the quantification of moulds, house dust mites, and green algae. The preliminary results indicated that at least in the 14 houses that had been examined in detail, damage due to dampness really meant internal mould sources. House dust mites were found only in low quantities in four houses, all of which had dampness spots (S Andrae, O Axelson, B Bjorkstén. Allergens in modern insulated houses Paper in preparation.)

HEALTH EFFECTS

The morbidity was influenced mainly by (a) residential area, (b) type of dwelling, (c) damage due to dampness in the house, and (d) parental smoking.

No effects on the morbidity were noted for children with current exposure in the house to furred pets (2327, 47%), cage birds (934, 20%), or aquarium fish (1098, 23%). For the final evaluation of each one of the first four factors mutual stratification was undertaken for control of the others.

(a) Residential area

The areas differed with regard to type of dwelling, with 209 (22%) in area 4 and 125 (9%) in area 2 living in apartments There were no major differences between the two areas concerning parental smoking 444 (46%) *v* 586 (44%), history of breast feeding for at least six months: 271 (29%) *v* 388 (30%); dampness damage in the house. 89 (9%) *v* 108 (8%), and living in a family with only one adult 51 *v* 70 (5% in both areas).

Area 4, which had the pulp and paper plant, had the highest prevalence of allergic rhinitis, allergic asthma, and prolonged coughing during upper respiratory tract infections (tables 3 and 4) There was a difference for all types of allergic asthma, but the difference was most noticeable for asthma during the birch pollen season, presumably indicating birch pollen induced asthma. For asthma and coughing the differences between the areas were most noticeable for children, 8 years and older, area 4 having the higher rates

(b) Type of dwelling

Children living in one-family houses—which indirectly reflected better social conditions in general—tended to have allergic symptoms more often than children living in apartments, although this was not significant. Children living in apartments had parents who smoked in 440 (55%) instances *v* 1689 (41%) instances for those living in one-family houses (p<0·001).

(c) Damage due to dampness in the house

Living in houses with damage due to dampness independent of family smoking habits was associated with a significantly increased occurrence of prolonged coughing after respiratory tract infections: 76 (19·0%) *v* 404 (9·1%); exercise-induced coughing: 36 (8·9%) *v* 253 (5·5%); allergic rhinitis: 38 (9·4%) *v* 308 (6·7%); and allergic asthma: 35 (8·7%) *v* 228 (5·0%). These environmental factors caused most noticeable effects in children having a family history of asthma with 23 (5·9%) occurrences

Table 3 *Crude occurrence of symptoms of bronchial hyperreactivity and allergic disease in the different areas (Figures are percentages)*

Area	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*All areas*
No of children	491	1329	263	953	214	1517	223	4990
Coughing >2 weeks during upper respiratory tract infections	8·5	8·2	8·8	**13·0**	9·5	9·6	9·6	9·7
Exercise induced cough	5·1	5·9	**7·3**	6·3	6·5	5·7	5·0	5·9
Allergic asthma (total)	5·0	5·5	3·4	**7·1**	5·6	4·3	5·8	5·3
Birch pollen induced asthma	2·6	2·5	1·0	**4·4**	3·3	2·5	1·4	2·8
Allergic rhinitis	7·9	6·7	4·9	**8·8**	8·4	6·6	2·7	7·0

The bold figures signify the highest value for each item

Table 4 *Mantel-Haenszel risk ratios for living in area 4 v area 2 at different ages, in total 12 strata. (Underlying stratification for parental smoking, damage due to dampness at home, and type of dwelling not shown)*

	Age interval			*p Value for 6 months to 16 years (95% confidence interval)*
	6 months–7 years	*8–16 years*	*6 months–16 years*	
Coughing >2 weeks during upper respiratory tract infection	1·3	1·8	1·5	<0·05 (1·4 to 1·6)
Exercise induced cough	1·0	1·0	1·0	NS
Allergic asthma (total)	1·0	1·5	1·3	NS
Birch pollen induced asthma	1·2	2·0	1·8	<0·001 (1·6 to 2·3)
Allergic rhinitis	1·3	1·3	1·3	<0·05 (1·1 to 1·6)

Table 5 *Mantel-Haenszel risk ratios showing combined effect of parental smoking and living in houses with damage due to dampness on bronchial hyperreactivity and allergic disease (Underlying stratification for residential area and type of dwelling not shown)*

	Parents not smoking		*Parents smoking*	
	Damage due to dampness not present (n=2581)	*Damage due to dampness present (n=212)*	*Damage due to dampness not present (n=1958)*	*Damage due to dampness present (n=187)*
Coughing >2 weeks during upper respiratory tract infection	1·0	1·9* (1·3 to 2·9)	1·3* (1·1 to 1·6)	2·8† (2·0 to 4·1)
Exercise induced cough	1·0	1·0	1·2	2·2† (1·4 to 3·5)
Allergic asthma	1·0	1·3	0·9	2·5† (1·5 to 3·7)
Birch pollen induced asthma	1·0	1·7	0·9	2·9† (1·5 to 5·5)
Allergic rhinitis	1·0	1·1	1·0	1·8* (1·1 to 2·8)

Level of significance *v* non-smoking and no dampness *p<0·05; †p<0·001. 95% Confidence intervals in parentheses of allergic asthma in children in houses undamaged by dampness (n=389) *v* 11 (20·4%) occurrences in children in houses damaged by dampness (n=54) ($p<0·001$) In children with no family history of asthma the numbers were 78 (1·9%) (n=4108) *v* 8 (2·4%) (n=336); this was not significant. The number of occurrences of allergic asthma were significant when children with and without a family history of asthma and not living in houses damaged by dampness were compared ($p<0·001$) and when children with and without a family history of asthma but who were living in houses damaged by dampness were compared ($p<0·001$). Even when asthma induced by house dust was excluded from the analysis the relation between environmental factors and allergic disorders was significant.

Type of house construction—for example, presence of a basement, did not influence the prevalence of any of the clinical symptoms in the children.

(d) Parental smoking

Children with parents who smoked had exercise induced cough more often than the children of nonsmokers: 150 (7·0%) *v* 143 (5·1%) ($p<0·01$). For children with parents who smoked, living in houses with damage by dampness, there was a noticeable increase in exercise induced cough, allergic rhinitis, and allergic asthma, particularly when compared with children not exposed to any of these factors but also in comparison with children exposed to only one of them (table 5 and fig 2).

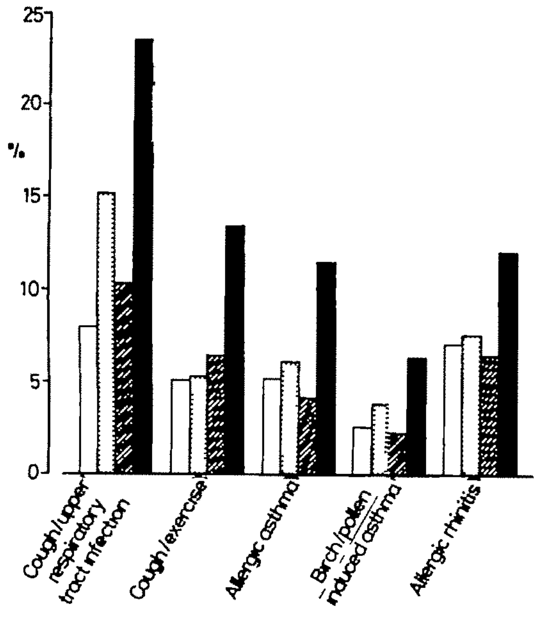

Fig 2 *Occurrence (%) of symptoms suggesting bronchial hyperreactivity and allergic disease in relation to parental smoking and damage due to dampness at home in 4938 children No parental smoking and no damage due to dampness □ (n=2581); no parental smoking and damage due to dampness ⬚ (n=212), parental smoking and no damage due to dampness ▨ (n=1948); and parental smoking and damage due to dampness ■ (n=187)*

Discussion

Children living in area 4—that is, in the neighbourhood of the pulp and paper mill—had symptoms of bronchial hyperreactivity and allergic diseases more often than children of the same age living in an area with little local pollution. Possible explanations for the findings include socioeconomic differences, overreporting in the area, climatic differences, and an irritating effect of industrial pollutants.

These differences remained significant even when type of dwelling, which was used as a crude measurement of socioeconomic differences, was accounted for by stratification. The fact that there was occasionally a pronounced smell of mercaptans in area 4 might have caused concern over discharge of air pollutants and a subsequent overreporting of health effects—that is, with regard to even minor symptoms On the other hand, the pulp plant is the sole major employer in the area and thus represents employment and prosperity for the local population, which may even have reduced the tendency to report symptoms. In the validation study, however, no signs of overreporting or underreporting were found when this area was studied in relation to other areas.

The differences between the two areas were greater for schoolchildren than for preschool children. If the recorded differences had merely been the result of overreporting no clear age difference would have been expected. It is even reasonable to assume that overreporting would have been more pronounced for the younger children as they spend more time at home and because the social consequences of disease in a young child are usually greater for the family than if the child is older.

Climatic differences between the areas could have been considered as an additional factor influencing the results but according to the Swedish Meteorologic and Hydrologic Institute in Norrkoping, these differences are minor, and the areas have in fact an almost identical climate. (K Persson, head of the Meteorologic Department of the Swedish Meteorologic and Hydrologic Institute. Personal communication.)

It seems reasonable to consider the symptoms as a possible effect of industrial pollution as there is no clear indication of other factors explaining the differences. In this context the occasional occurrence of high concentrations of sulphur dioxide are particularly interesting as it is well known that sulphur dioxide in high concentrations causes irritation of human mucous membranes.[10] Moreover, in animal experiments sulphur dioxide has been shown to enhance IgE antibody formation.[11] Other undefined pollutants, however, may also have contributed

The findings that children living in homes damaged by dampness more often had signs of bronchial hyperreactivity and allergic disease cannot fully be explained. Localised damage caused by dampness in a house often leads to mould formation. The amount of this internal mould growth as well as the species concerned may vary. Increased humidity may also be associated with increased number of house dust mites.

Moulds are known to cause allergic reactions but they may possibly, in addition, have other effects on the airways as indicated by a recent report in which there was a correlation between upper respiratory tract symptoms in adults and exposure to aspergillus moulds in the homes.[15]

The effect of living in a damp house as related to the occurrence of allergic asthma was particularly obvious for children with a family history of atopic disease. This was true not only for 'dust' allergy, but also for allergy to birch pollen, which has a well defined season, indicating an unspecific environmental effect on the airways in children. Consistent with our findings are those reported of an increased prevalence of symptoms, presumably induced by mould exposure, in smokers compared with non-smokers in adults.[15]

Children living in area 4 had a higher prevalence of symptoms of bronchial hyperreactivity and allergy than children living in other areas A possible confounding factor concerning the effect of residential area is the fact that the school building for children, age 7–11 years, in area 4 had a serious mould problem. This cannot, however, explain the higher than expected morbidity in preschool children.

In conclusion, this questionnaire survey indicates that exposure to tobacco smoke in the home, housing conditions, and even moderate environmental pollution from a pulp and paper factory may all affect the respiratory tract of children. This in turn may lead to signs of bronchial hyperreactivity and respiratory allergy in some children. The effects of these environmental factors appear to be synergistic.

This study was supported by grants from the Konsul Th Berg Foundation, the Annual Campaign of First of May Flower, the Åhlén Foundation, and the County Council of Östergotland

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Accepted 15 December 1987

Archives of Disease in Childhood, 1988, **63,** 479–483

Nebulised salbutamol does have a protective effect on airways in children under 1 year old

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SUMMARY Ten infants under the age of 1 year each of whom gave a history of recurrent wheezing attacks were studied with a total body plethysmograph. All the infants were free of wheeze when studied and were sedated with chloral hydrate. All 10 showed a significant deterioration in lung function when given nebulised water for two minutes with an increase in airways resistance and a decrease in specific conductance at one and five minutes after nebulisation compared with baseline readings. Measurements returned to baseline values within 15 minutes. When the same amount of nebulised water was given 20 minutes after nebulised salbutamol, however, there was no significant deterioration in lung function at one and five minutes after administration of nebulised water.

We conclude that the airways were protected against the bronchoconstricting effect of nebulised water by the β_2 adrenoreceptor stimulant salbutamol.

Many doctors believe that β_2 adrenoreceptor stimulants have little or no effect on the airways of infants under the age of 1 year. These children do, however, have β_2 adrenoreceptors[1] and smooth muscle[2] in their airways and theoretically should respond to β_2 adrenergic stimulants. Nebulised water has a bronchoconstricting effect on asthmatic children and adults,[3–7] and we have found that it also causes bronchoconstriction in wheezy infants (unpublished data).

The present study was designed to find out if nebulised salbutamol protects the airways of wheezy infants Nebulised water was used as a bronchoconstricting challenge.

Patients and methods

Patients studied were under 1 year old and attending this hospital for routine assessment. All had had more than two wheezy episodes in the preceding months. Table 1 shows their age, sex, and history of bronchiolitis At the time of the study all were clinically well and at least four months had elapsed since their bronchiolitic illnesses. Each study was done in the outpatient clinic, all patients were awake, and allowed home within three hours of arrival.

The infants were sedated with chloral hydrate (120 mg/kg), and thoracic gas volume and airways resistance were measured with total body plethysmography.[8–11] The total body plethysmograph had a capacity of 260 litres, and a servo controlled heating system maintained the face mask, shutter system, and rebreathing bag at 36°C. Thoracic gas volume was measured at the end of inspiration, and the tidal volume was subtracted before calculation. The children were nursed supine and firm latex masks applied to their faces. The dead space of each mask was 88 ml There was a bias flow of air at 5 l/minute to the face mask Signals were relayed to the axis of a cathode ray oscilloscope, all readings were made by the same observer,

Table 1 *Details of 10 infants studied*

Patient No	*Age (months)*	*Weight (kg)*	*Sex*	*History of bronchiolitis*
1	11	10·5	Male	Yes
2	10	9·1	Male	No
3	9	8·3	Female	Yes
4	9	8·0	Male	No
5	9	10·2	Male	Yes
6	10	8·9	Female	Yes
7	6	8·3	Male	Yes
8	9	8·2	Male	Yes
9	10	11·0	Male	Yes
10	11	11·2	Female	No

and calculations were made by standard techniques. Multiple breaths were analysed in each case. Baseline measurements of thoracic gas volume and airways resistance were calculated.

The infants were then given water nebulised ultrasonically at a temperature of 21°C from an Intersurgical Variosonic II nebuliser at setting number 3 through the face mask for two minutes with a flow rate of 5 l/minute. Thoracic gas volume and airways resistance were measured at regular intervals until they were stable (which was defined as no change in readings over a five minute period) The dense mist occasionally escaped from the spac between mask and face owing to an inadequate sea during the first few seconds of nebulisation. Th mask was adjusted accordingly and the study re started with an adequate seal. The infant was the given salbutamol (0·5 ml salbutamol respirato solution in 1·5 ml normal saline) through a Cirrhu nebuliser chamber at a flow rate of 6 l/minute fo five minutes. Thoracic gas volume and airway resistance were measured at regular intervals unt they had returned to baseline measurements. Neb ulised water was then given through the ultrasoni

Table 2 *Baseline readings in airways resistance and specific conductance, and changes after two minute challenge with nebulised water in 10 infants*

Patient No	*Baseline readings*			*Time after challenge (minutes)*					
				1		*5*		*10*	
	Thoracic gas volume ml/kg	*Airways resistance*	*Specific conductance*	*Airways resistance*	*Specific conductance*	*Airway resistance*	*Specific conductance*	*Airway resistance*	*Specific conductance*
1	17	17·2	0·31	25·8	0·21	33·1	0·16	17·2	0·31
2	31	23	0·15	27·6	0·14	32·2	0·12	23·7	0·16
3	25	21	0·22	21·3	0·23	30·9	0·17	25·6	0·20
4	28	21	0·21	22·0	0·20	27·4	0·17	21·0	0·21
5	32	22	0·15	27·3	0·10	28·8	0·10	21·8	0·14
6	33	21·5	0·15	27·6	0·12	33·7	0·10	25·0	0·13
7	39	15·5	0·22	20·3	0·17	25·3	0·14	20·0	0·17
8	65	17	0·12	20·3	0·10	21·4	0·10	17·3	0·12
9	38	21	0·11	24·8	0·09	27·4	0·08	20·9	0·11
10	17	21·0	0·25	32·0	0·15	40·7	0·12	21·0	0·25
Mean (SD)	32·5 (12)	20·1 (2·5)	0·19 (0·05)	25·0 (3·8)	0·15 (0·05)	30·1 (5·0)	0·12 (0·03)	21·3 (26·0)	0·18 (0·05)

Airways resistance is reported as cm H_2O/l/second
Specific conductance is reported as cm $H_2O^{-1}s^{-1}$

Table 3 *Baseline readings in airways resistance and specific conductance, and changes after two minute rechallenge given 20 minutes after nebulised salbutamol in 10 infants*

Patient No	*Baseline readings*			*Time after rechallenge (minutes)*			
				1		*5*	
	Thoracic gas volume ml/kg	*Airways resistance*	*Specific conductance*	*Airways resistance*	*Specific conductance*	*Airways resistance*	*Specific conductance*
1	17	17·2	0·31	17·2	0·37	17·1	0·37
2	29	23·7	0·16	23·0	0·16	23·0	0·16
3	23	21·3	0·23	23·8	0·22	23·8	0·22
4	28	21·0	0·21	20·5	0·28	20·4	0·22
5	32	21·3	0·14	14·2	0·22	14·1	0·22
6	32	25·0	0·13	21·0	0·16	21·0	0·16
7	39	15·4	0·22	15·5	0·23	15·4	0·22
8	61	17·3	0·12	16·8	0·12	16·5	0·12
9	38	20·9	0·11	20·1	0·11	20·2	0·13
10	17	21·0	0·25	20·5	0·26	20·5	0·26
Mean (SD)	31·5 (12)	20·4 (2·5)	0·18 (0·05)	19·0 (3·4)	0·2 (0·05)	19·2 (3·3)	0·19 (0·04)

Airways resistance is reported as cm H_2O/l/second
Specific conductance is reported as cm $H_2O^{-1}s^{-1}$

nebuliser for two minutes as described previously. Thoracic gas volume and airways resistance were measured until they were stable. Each infant was monitored continuously with an oxygen saturation machine and an electrocardiogram. Specific conductance was calculated from the readings taken. A paired *t* test was used to analyse the results.

The study was approved by the Nottingham University ethics committee. Informed parental consent was obtained for each of the studies.

Results

Baseline measurements of thoracic gas volume, airways resistance, and specific conductance are shown in table 2 together with the changes in airways resistance and specific conductance after the administration of nebulised water. All infants showed significant increases in airways resistance one minute after the water had been given ($p<0{\cdot}01$) and five minutes after it had been given ($p<0{\cdot}001$); these had returned to baseline values after 10 minutes (fig 1). There were also significant decreases in specific conductance one minute after the water had been given ($p<0{\cdot}01$); and five minutes after it had been given ($p<0{\cdot}001$); these had returned to baseline values after 10 minutes (fig 2).

When rechallenged with a similar amount of

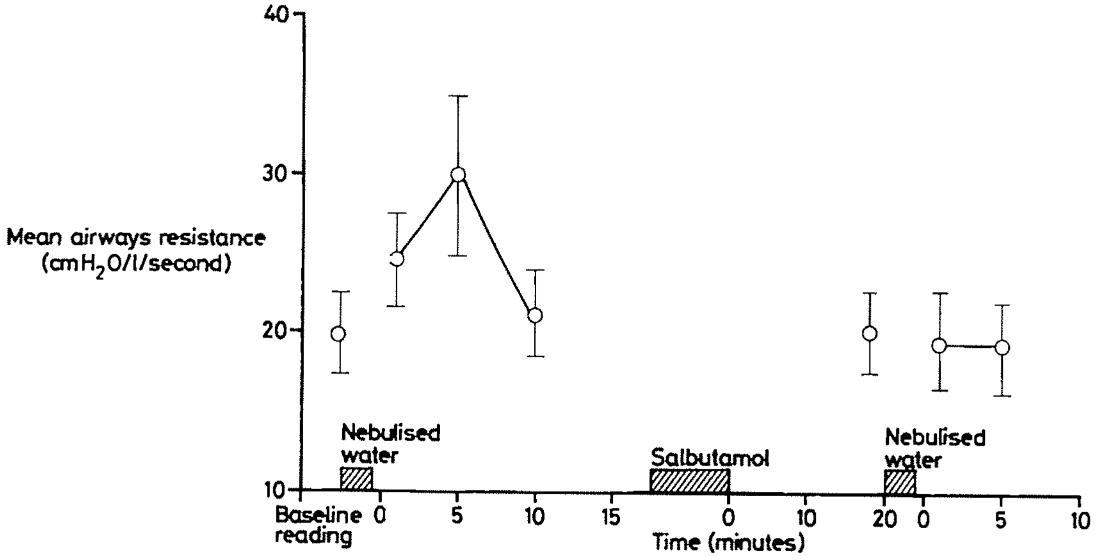

Fig 1 *Mean (SD) airways resistance of 10 infants with history of wheezing showing changes after the administration of nebulised water and salbutamol*

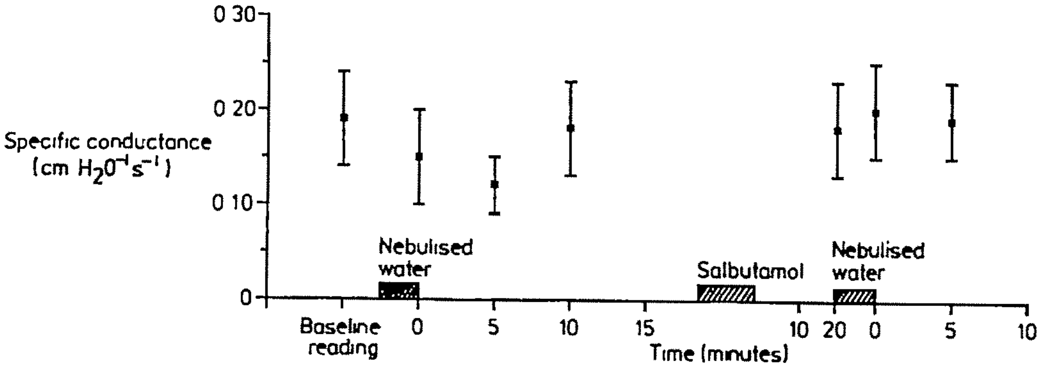

Fig 2 *Mean (SD) specific conductance of 10 infants with history of wheezing showing changes after the administration of nebulised water and salbutamol.*

nebulised water 20 minutes after nebulised salbutamol had been given however, there were no significant changes in airways resistance (p>0·5) or specific conductance (p>0·5) (fig 1). There were no significant changes in thoracic gas volume after any of the challenges.

There were no abnormalities in the electrocardiographic traces, and oxygen saturation did not fall below 84% in any of the patients during the study.

Discussion

Subjective clinical observations have suggested that nebulised bronchodilators are helpful in treating some wheezy infants. There is little evidence from clinical trials, however, to recommend treatment of such infants with bronchodilators.[12-23]

Nebulised water produces bronchoconstriction in asthmatic subjects.[3-7] In the 10 infants we studied all of whom had history of wheezing, we confirmed that nebulised water in the regimen we gave caused bronchoconstriction. The measurements showing deterioration in lung function correlated well with the patients' clinical signs during the study. When rechallenged with the same amount of nebulised water 20 minutes after receiving nebulised salbutamol, however, there was no evidence of bronchoconstriction; the salbutamol had protected the airways.

Prendiville *et al* studied five infants and found that salbutamol had a similar protective effect when histamine was used as the challenge.[1] The results of this and the present study show that β_2 adrenoreceptors do exist in infants.

The amount of nebulised water given is derived from the results of 20 studies we performed before this trial (unpublished data) We found that repeated stimuli with nebulised water also produced bronchoconstriction. This suggested that the lack of response to the administration of nebulised water after being given salbutamol was not because there was a refractory period after the original bronchoconstricting challenge. Hypo-osmolar solutions cause the release of histamine from mast cells[24] and we presume that this may be the cause of the bronchoconstriction seen in our infants, the histamine acting either directly on the smooth muscle or by reflex action on the vagus nerve.

During the studies some of the infants seemed clinically worse immediately after the administration of salbutamol. After completing the study we looked at a further 17 infants all of whom gave a history of wheezing.[25] In 13 of the 17 infants there was a rise in airways resistance and a fall in specific conductance when they were challenged with nebulised water. They also showed significant increases in airways resistance and decreases in specific conductance after nebulised salbutamol had been given We feel this may have been partly caused by the acid and preservatives in the solution. Until we have found out the specific cause of the paradoxical deterioration and how to eliminate it we cannot recommend the use of nebulised salbutamol at home for infants under 1 year old.

The validity of thoracic gas volume measurements in wheezy infants has recently been questioned by Godfrey *et al.*[26] They found low thoracic gas volume measurements in wheezy infants who had had bronchiolitis that were difficult to explain. In some of our patients the measurements were surprisingly low, and they changed remarkably little during the challenge procedures.

We used the plethysmograph to look for changes in the airway function of our infants and we feel that this is a valid use of it.

We thank the Asthma Research Council of the United Kingdom for financial support

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Accepted 25 October 1987

Archives of Disease in Childhood, 1988, **63,** 484–490

Growth and endocrine function in steroid sensitive nephrotic syndrome

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SUMMARY Longitudinal height data and physical development were assessed in 29 boys and 12 girls taking long term steroid treatment for steroid sensitive nephrotic syndrome. Growth in both boys and girls, assessed by changes in height standard deviation score (ΔHt SDS), worsened significantly with chronological age. There was a significant negative correlation between ΔH SDS and duration of treatment in boys, but not in girls. There was no correlation between ΔH SDS and relapse rate or the use of cyclophosphamide. In the boys, Ht SDS decreased significantly only after the age of 10 years and was associated with delay in the appearance o secondary sexual characteristics.

Eight adolescent boys were assessed endocrinologically by an overnight hormone profile Blunting of the pulsatility of growth hormone and gonadotrophins was seen in six. Norma profiles were seen in two subjects who were both off steroid treatment at the time of study

Abnormal endocrine function in adolescent boys treated long term for steroid sensitive nephrotic syndrome corresponded with the clinical picture of delayed onset of puberty, which accounted for severe growth retardation in a substantial proportion of subjects.

The adverse effects of steroid treatment on growth have been related to both dosage and duration of treatment.[1-3] Many children with steroid sensitive nephrotic syndrome receive steroid treatment for several years and in many cases treatment continues throughout adolescence.[4] Current practice for long term treatment is to use a single dose of prednisolone on alternate mornings. This regimen has been suggested to minimise growth retardation and to leave final height unaffected[5-7]; 'catch-up' growth has been reported after treatment is stopped.[8]

We have observed, however, several adolescents taking long term alternate day steroids for steroid sensitive nephrotic syndrome who were significantly short or whose sexual maturation was delayed, or both, and who, as a result, were severely emotionally disturbed. Retrospective analysis of the longitudinal growth patterns of subjects currently attending our paediatric renal clinic with this syndrome, suggested that after the age of 10 years maturational delay was a prominent clinical feature. We therefore investigated the endocrine function of boys with steroid sensitive nephrotic syndrome in an attempt to determine the site of action of steroids on the hypothalamic–pituitary–gonadal axis, which ma account for delayed puberty and subsequent shor stature.

Patients and methods

All the subjects with steroid sensitive nephroti syndrome who were steroid dependent and attende Guy's Hospital paediatric renal clinic between Jul 1984 and January 1986 were included in the stud (total 41: 29 boys, 12 girls). Relapses of proteinuri were treated with prednisolone (60 $mg/m^2/day$) an maintenance steroids were given on alternate day at the dose found to be necessary to keep the urin protein free. An eight week course of cyclophosphamide (2·5–3 mg/kg/day) was given to children wh required unacceptably high doses of maintenanc steroids to prevent relapse. All subjects had norma plasma creatinine concentrations.

The following were obtained from the notes an at examination.

(1) Chronological age (year) at diagnosis, a first clinic visit to Guy's Hospital (14 boys an four girls were seen initially at other hospitals)

and at most recent height measurement (table 1).

(2) First available height measurement at Guy's Hospital (first Ht) and subsequently at yearly intervals until the most recent examination or at the time of stopping steroid treatment (last Ht). Height was measured by the clinic nurse using a Harpenden stadiometer. For each height (cm) the height standard deviation score (Ht SDS) was calculated according to the formula, Ht SDS=x−x̄/SD, where x̄ and SD are the age matched population mean height and standard deviation respectively and x is the patient's height (population data according to Tanner *et al*[9]).

(3) Duration of treatment calculated as the number of years on steroid treatment between first and last height measurements (table 1).

(4) The number of relapses between first and last height measurement. A relapse was defined as an episode of proteinuria treated with an increase in prednisolone treatment to 60 mg/m^2/day.

(5) The number of courses of cyclophosphamide treatment.

(6) Pubertal staging (according to Tanner[10]) in those patients still attending Guy's Hospital.

Statistical differences between first and last Ht SDS were analysed by comparison of 95% confidence intervals. The change in Ht SDS from first to last measurements (ΔHt SDS) was correlated with age at final examination, duration of treatment, and the relapse rate by Pearson's product-moment correlation coefficient. The Mann–Whitney U test was used to compare ΔHt SDS in those children treated and those not treated with cyclophosphamide; to compare both the relapse rate and the change in Ht SDS before and after the age of 10 years; and to compare ΔHt SDS in boys age less than 8 years at final examination with boys who began treatment after the age of 8 years. Results are expressed as mean (SD).

An overnight hormone profile study was performed in eight adolescent boys who were short or delayed in puberty, or both. Three boys were off steroid treatment and clinically well with no proteinuria. Each study commenced at 1800 hours, when an indwelling cannula was inserted into a forearm vein. Adequacy of sleep was analysed using a portable continuous electroencephalograph (Oxford Medilog System).[11] Blood samples were taken every 20 minutes from 2000 hours through to 0700 hours (3 ml blood per sample). Plasma was subsequently stored at −20°C until assay. Growth hormone (mU/l) and gonadotrophins (luteinising hormone and follicle stimulating hormone IU/l) were measured in each sample and testosterone (nmol/l) and insulin like growth factor I (IGF–1, U/ml) in intermittent samples throughout the night. All samples from each profile were batch analysed.

Growth hormone was measured by radioimmunoassay using the first International Reference Preparation (IRP) reference 66/217, with intra-assay coefficient of variation of 5·0% and 2·4% at 10·8 and 20·4 mU/l respectively and interassay coefficient of variation of 10·1% at 7·5 mU/l. Gonadotrophins were measured by radioimmunoassay using the first IRP reference of luteinising hormone, 68/40 and follicle stimulating hormone, 78/549, with an intra-assay coefficient of variation of (a) luteinising hormone, 8·3% and 10% at 2·4 and 15·0 IU/l, respectively and (b) follicle stimulating hormone, 10·3% and 7·3% at 2·8 and 14·9 IU/l; testosterone was measured by radioimmunoassay using a standard kit method (Diagnostic Products Corporation). Serum IGF–1 was measured by radioimmunoassay after acid-ethanol extraction.[12] Antiserum R557A and ^{125}I–IGF–1[13] were kindly provided by Dr D J Morrell (Institute of Child Health, London). Intra-assay and interassay coefficients of variation were <8% and <10% respectively IGF–1 values are expressed as potency relative to pooled normal adult human reference serum defined as 1 unit IGF–1/ml.

Growth hormone and gonadotrophin hormone peak analysis was performed both visually and using the 'Pulsar' programme[14] which was modified locally to include a calculation of area under the curve by summation of trapezoids. Statistical comparison of the association of overnight profile measurements

Table 1 *Median (range) age at diagnosis and at first and last examination and duration of treatment*

	Boys (n=29)	*Girls (n=12)*
Age at diagnosis (years)	3·1 (1·3–13·5)	3·0 (1·6–9·0)
Age at first height measurement (years)	4·3 (2·0–13·6)	3·5 (1·6–7·8)
Age at last height measurement or on stopping steroids (years)	13·1 (3·5–18·6)	7·3 (4·1–12·9)
Duration of treatment over which heights known (years)	6·2 (0·2–11·5)	3·6 (0·6–9·2)

Table 2 *Mean height standard deviation score (Ht SDS) for boys and girls at first and last examination compared with expected normal population data*

	No of patients	*Mean (SD)*	*95% Confidence intervals*	*Normal population*	
				t	*p Value*
Boys: first	29	−0·39 (1·20)	−0·84 to 0·07	−2·10	0·05
last	29	−0·86 (1·20)	−1·31 to −0·41	−4·63	<0·001
Girls: first	12	−0·39 (0·74)	−0·86 to 0·08	−1·83	0·09
last	12	−0·49 (0·73)	−0·96 to 0·02	−2·34	0·04

with other hormone values and staging of puberty was made by calculation of Pearson product-moment correlation coefficient.

Results

The mean Ht SDS for the first and last examination compared with normal population data is shown in table 2.[9] There was a significant fall in the Ht SDS for the boys (ΔHt SDS −0·47, 95% confidence intervals −0·84 to −0·11, df 28, t −2·66, p<0·02) but not for the girls (ΔHt SDS, −0·10, 95% confidence intervals −0·44 to 0·24, df 11, t −0·66, p=0·5).

There was a significant negative correlation between ΔHt SDS and age at final examination (boys, r=−0·50, p<0·01, girls r=−0·61, p<0·05); (fig 1).

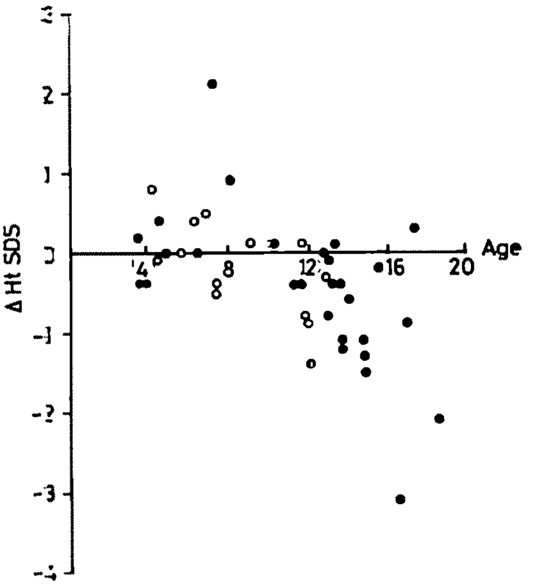

Fig 1 *Relation between age (in years) at last examination and change in height standard deviation score (ΔHt SDS) in boys (●) and girls (○).*

There was also a significant negative correlation between ΔHt SDS and duration of treatment (fig 2) for the boys (r=−0·64, p<0·01) but not the girls (r=−0·24, p=0·5). Only three girls, however, had been treated for more than five years.

To attempt to clarify the relative effects of age and duration of treatment we examined the data longitudinally. The ΔHt SDS from first height at roughly yearly intervals is shown in fig 3. The mean fall in Ht SDS after the age of 10 years until final examination was significantly greater than the fall in Ht SDS from first height measurement until the age of 10 years for the boys (*F*=10·25, p<0·01), but the difference was not significant for the girls (*F*=4·06, p<0·1). Only five boys developed steroid sensitive nephrotic syndrome over the age of 8 years (mean 11·0 years, range 8·1–13·6) and required treatment until they were over 13 years; their mean age at final examination was 14·6 years (range 13·3–16·4) and mean ΔHt SDS was −0·6 (range −0·3 to −1·1). There were seven boys who were less than 8 years

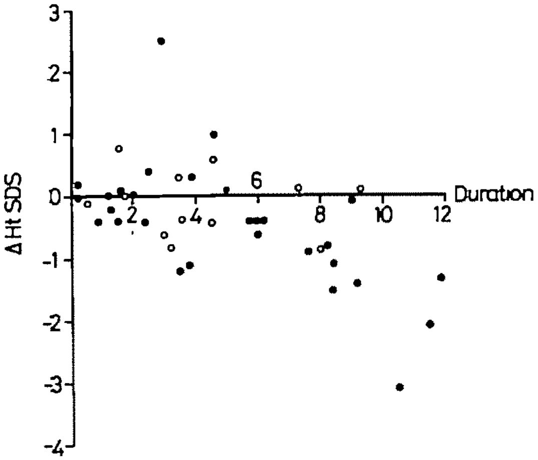

Fig 2 *Relation between duration of treatment (in years) and change in height standard deviation score (ΔHt SDS) in boys (●) and girls (○).*

old at final examination (mean 4·9 years, range 3·5–7·9) who had been treated for a mean of 1·9 years (range 0·5–4·0). Their mean ΔHt SDS was +0·3 (range −0·4–2·1). ΔHt SDS was significantly less for those diagnosed under 8 years of age than for the boys diagnosed after the age of 8 years (F=6·24, $p<0·05$).

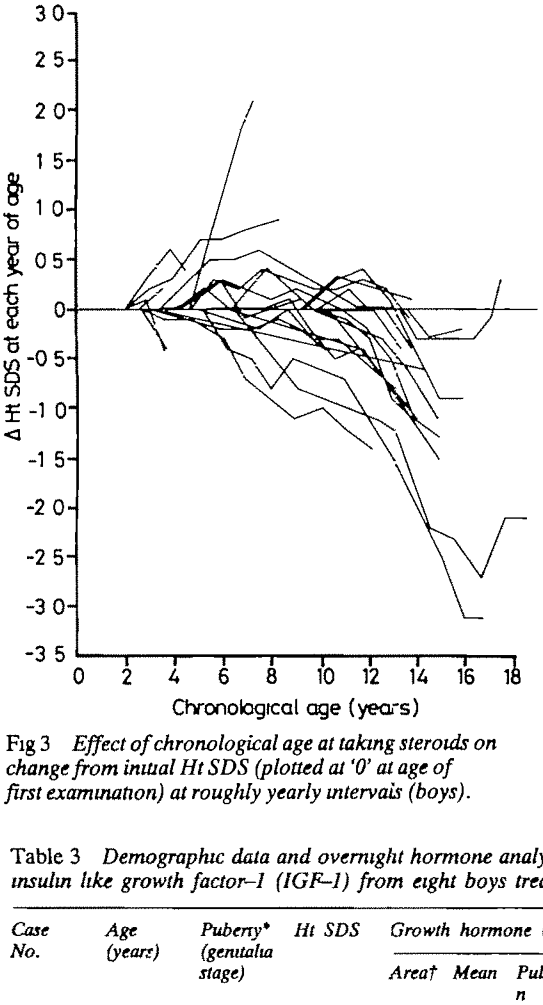

Fig 3 *Effect of chronological age at taking steroids on change from initial Ht SDS (plotted at '0' at age of first examination) at roughly yearly intervals (boys).*

There was no relation between ΔHt SDS and the relapse rate for the boys (r=0·26, p=0·5) or the girls (r=0·23, p=0·5). The relapse rate was significantly greater before the age of 10 years for the boys (F=6·44, $p<0·05$) but was unchanged in the girls (F=0·01, $p>0·1$). There was no difference between the mean ΔHt SDS for boys treated with cyclophosphamide (−0·79 (1·03), n=12) compared with those treated only with steroids (−0·10 (0·78) n=17), (F=2·67, $p<0·1$)

Puberty was assessed in all the subjects and a comparison was made with the expected age at the appearance of secondary sex characteristics.[10] Nine boys were delayed (mean age 15·2 years, range 14·1–16·7) with pubic hair and genital stages at less than the third centile, and testicular volume was between 4 and 10 ml in seven. The three girls over the age of 12 years were progressing normally through puberty.

Demographic data and hormone profile analysis of the eight boys is given in table 3. All subjects slept throughout the study with normal electroencephalographic sleep patterns.[11] Data of hormone profiles from a control group were lacking. Various studies over the last 15 years, however, have suggested a noticeable increase in pulsatility of growth hormone and gonadotrophins during the age range associated with normal puberty.[15–19] Visual comparison with these documented hormone profiles suggested that six of the eight subjects had an abnormal blunting of their overnight profiles, with a decrease in pulse amplitude but not pulse number. A typical example of a blunted profile is shown (fig 4a). Two of the boys not receiving steroids had higher concentration of hormones during the night as assessed visually and by pulse analysis (table 3). One of the boys, the subject who had been off steroids for two years, had exceptionally high concentrations of growth hor-

Table 3 *Demographic data and overnight hormone analysis of growth hormone, luteinising hormone, testosterone, and insulin like growth factor–1 (IGF–1) from eight boys treated with long term steroid treatment for nephrotic syndrome*

Case No.	*Age (years)*	*Puberty* (genitalia stage)*	*Ht SDS*	*Growth hormone (mU/l)*				*Luteinising hormone*				*Mean testosterone (nmol/l)*	*Mean IGF–1 (U/ml)*
				Area†	*Mean*	*Pulses n*	*Pulses amplitude*	*Area*	*Mean*	*Pulses n*	*Pulses amplitude*		
1	15·4	3	−2 01	326	5·4	5	7 2	159	2 7	5	2·0	3·6	1·5
2	14 8	2	−2 44	457	7·5	3	22 2	335	5 5	5	4·1	7 3	1·4
3	17 2	3	−3 06	327	5·4	3	16·7	275	4 6	6	3·3	13 4	1 9
4	15 8	5	−1·01	2450	40·4	5	69 9	325	5·4	6	4·6	24·7	1 9
5	18·6	4	0 35	297	5·1	4	12 4	284	4 7	5	3·8	21 7	1 9
6	14·1	2	−0·10	237	4·0	4	8 0	410	6 7	6	5·5	7 1	2 4
7	13 3	2	−2·41	480	7·8	4	13 8	124	2·1	1	1·1	0·6	2 1
8	15·1	3	−2·60	529	9·4	5	21 5	289	4 2	3	2 0	6·7	2 7

*According to Tanner [10]
†Units of area under the curve=mU/l min per hour of study.
Cases 2, 4, 6 were off steroids for 0 5, 2 0, and 0 2 years, respectively

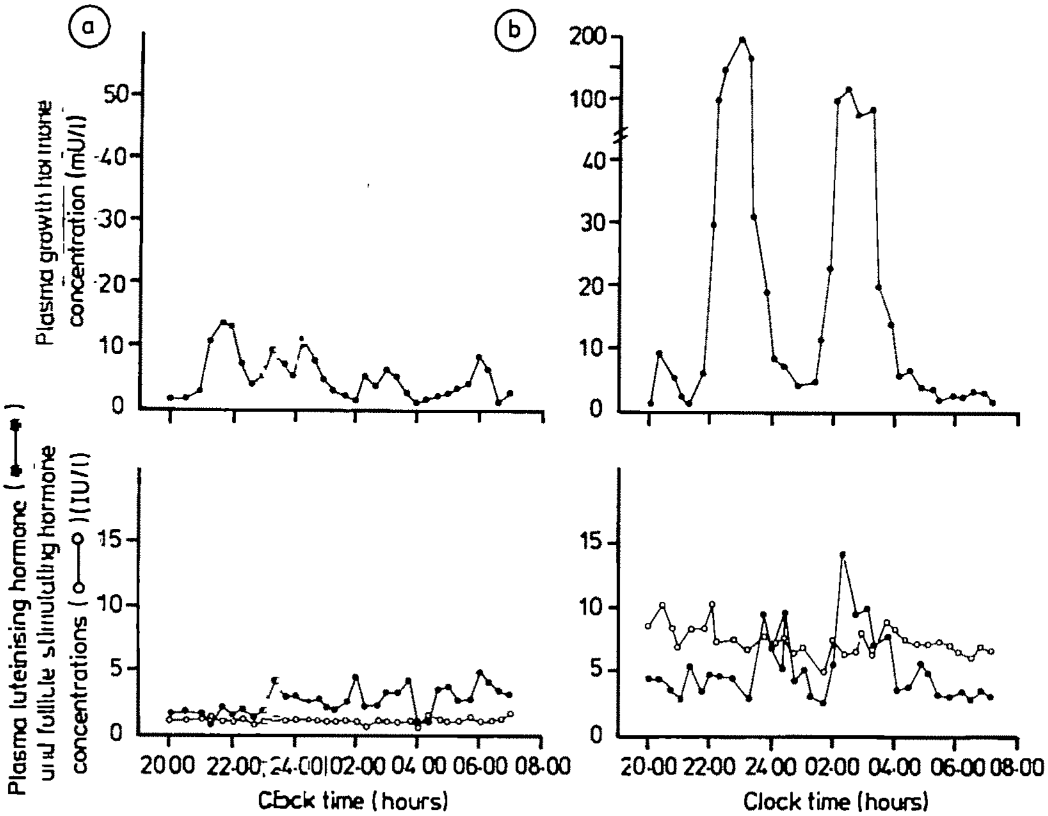

Fig 4 *Overnight hormone profile in two adolescent boys with steroid sensitive nephrotic syndrome: (a) patient 1, table 3, on continuous treatment since 2·3 years of age, (b) a boy (age 15·8 years) treated from 3·4 years of age, the steroids had been stopped two years previously*

mone and gonadotrophins and his profile is also shown (fig 4b).

Mean testosterone concentration was significantly associated with genital stage (r=0·82, p=0·013), as was growth hormone area under the curve (r=0·74, p=0·037). Mean growth hormone amplitude correlated with genital stage but this failed to reach significance at the 5% level (r=0·68, p=0·063). Mean growth hormone amplitude was associated positively with mean testosterone concentration, but this again failed to reach significance (r=0·66, p=0·076). Mean IGF-1 concentration was within our accepted normal range for this age with no association between IGF-1 concentration and with measurements of growth hormone or with testosterone concentration.

Discussion

We have shown that long term steroid treatment given through adolescence has an adverse effect on the rate of growth in boys with steroid sensitive nephrotic syndrome despite the use of a low dose alternate day regimen for the major part of the treatment course. We cannot say if this is also true for girls, who have a lower incidence of the syndrome and who, in our experience, require shorter treatment periods.

In boys, Ht SDS was significantly lower after several years of treatment, confirming data from previous studies.[2 3] Other studies have found the effect on growth to be dose related.[1 2 3 6] We were unable, in retrospect, to calculate accurately total steroid dose received by each child. If we make the assumption (although we have no statistical data) that the relapse rate reflects the total annual steroid dose, we can find no relation between this and growth retardation.

With increasing chronological age Ht SDS calculated at yearly intervals decreased (fig 3). Obviously it is difficult to disentangle duration of treatment and total steroid dose from an age dependent effect as many of the peripubertal children will have been taking steroids for longer. The beginning of a fall in growth velocity at the age of 10 years, however, and its sudden and sharp decline in all the boys at the age of 13 years, combined with the high incidence of delayed appearance of secondary sex characteristics, is strong evidence in favour of an independent effect of steroids on the onset and progression of puberty and the pubertal growth spurt. The pubertal delay is unlikely to be due to the steroid sensitive nephrotic syndrome itself as the children remain free from disease as long as they are having steroid treatment. Furthermore, we have been unable to show a relation between the relapse rate (which we believe is a reflection of the severity of the syndrome) and the ΔHt SDS In fact, over the age of 10 years the relapse rate is significantly less than before that age, whereas the major effect on growth was seen after 10 years.

We showed no relation between cyclophosphamide and growth problems. Foote *et al* found no effect of cyclophosphamide on growth,[8] but it is recognised that it may cause gonadal damage, particularly in boys [20] Low plasma androgens but normal gonadotrophins have been reported after a standard single course for steroid sensitive nephrotic syndrome.[21] Children given cyclophosphamide, however, are usually those showing severe steroidal side effects, so it may be possible to attribute these findings to either drug.

We do not know whether the boys will ultimately reach their genetic height potential. Kerrebijn and De Kroon reported slow and variable catch up growth after stopping steroid treatment in six prepubertal children with asthma.[3] Trompeter *et al* found the mean height to be between the 10th and 25th centiles respectively in six males and four females with steroid sensitive nephrotic syndrome who continued to relapse into adult life.[4] Foote *et al* found no significant difference in Ht SDS between 28 postpubertal and 52 prepubertal subjects treated with steroids for the syndrome and the general population, although there were six subjects with Ht SDS of less than −2 SD.[8] No information was given as to the number taking steroids during the peripubertal period and the data were not analysed longitudinally. Even if catch up growth was ultimately to occur this is of little consolation to many older boys who may be severely emotionally disturbed by loss of height and physical immaturity relative to their peers.

Overnight profile analysis suggested that steroid treatment considerably affects physiological secretion of hormones, with reduction in pulse amplitude of growth hormone and gonadotrophins. Stopping steroid treatment increases the growth hormone and gonadotrophin concentrations with an increase in the hormone pulse amplitude. The parameters of pulse analysis correlated with mean testosterone concentration and the clinical staging of puberty. No effect was seen on IGF–1 concentration. Men taking long term steroids for asthma have been shown to have significantly reduced levels of testosterone[22]; however, gonadotrophin concentrations have been reported either as normal[23] or increased.[22] Our data appear to be the first where physiological patterns of gonadotrophin secretion seem to be abnormally blunted during long term steroid treatment, although blunting of growth hormone pulsatility has been described.[24 25] It has been suggested that the mechanism of growth failure in steroid treatment is through a peripheral action of steroids at the level of the chondrocyte.[26] Our data from adolescents on long term steroid treatment for nephrotic syndrome suggest that central effects of steroid treatment on the hypothalamic–pituitary axis may be as important in this condition and certainly warrants further investigation.

In summary, we observed that boys with steroid sensitive nephrotic syndrome, who were treated with an alternate day steroid regimen for several years, do not maintain a normal rate of growth. As the growth delay occurs after the age of 10 years and is associated with delayed appearance of secondary sexual characteristics, we suggest that steroids interfere with the onset and progression of puberty and the pubertal growth spurt. Despite the evidence in the literature that final height is usually acceptable, this is a definite clinical problem with associated emotional difficulties. Overnight hormone profile analysis suggests that there is a disturbance of the hypothalamic–pituitary–gonadal axis with blunting of the expected overnight pulsatility of growth hormone and gonadotrophins. A disturbance of hypothalamic–pituitary function may be the major factor in the development of maturational delay and in severe cases this may be amenable to therapeutic agents such as luteinising hormone releasing hormone or anabolic steroids.

This study was supported by the Children's Nationwide Medical Research Fund SAG is supported by the Wellcome Foundation, PA by grants from Serono Laboratories (UK) and the Child Growth Foundation, and JJ by a grant from the Adint Trust We are grateful for Dr C Buchanan for performing the IGF–1 assay, to Mrs Jenkins and Miss G Wilson for the electroencephalography recordings and the sister and nursing staff of Peter Bishop medical ward. We thank Mrs Catherine Bryant for typing the manuscript

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Accepted 8 December 1987

Archives of Disease in Childhood, 1988, **63,** 491–494

Contribution of dose and frequency of administration to the therapeutic effect of growth hormone

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SUMMARY Forty two prepubertal children who were growth hormone insufficient were treated for the first time with 12 IU of biosynthetic methionyl growth hormone a week in three subcutaneous regimens for one year after one year of pretreatment observation. Thirteen received 4 IU growth hormone three days a week (group 1), 21 received 2 IU six days a week (group 2), and eight received 1 IU twice daily six days a week (group 3). The mean (SD) changes in height velocity standard deviation score (SDS) were +3·8 (1·7) in group 1, +5·3 (2·6) in group 2, and +5·9 (2·7) in group 3. There was a highly significant relation between the change in height velocity SDS and pretreatment height velocity SDS with a significant difference between the response of subjects receiving <15 IU/m²/week or >15 IU/m²/week growth hormone. Age, bone age, height SDS, and height for bone age SDS did not contribute to the prediction of response during the first year of treatment.

We recommend that growth hormone should be given in a dose of at least 15 IU/m²/week by equally divided daily subcutaneous injections.

Growth hormone treatment is effective in initially increasing and subsequently maintaining the growth velocity of children who secrete little growth hormone and grow poorly as a consquence.[1] Several groups have tried to elucidate the parameters that influence the growth response to treatment, which include the dose of growth hormone and frequency of administration, pretreatment growth velocity, age, bone age, height at the start of treatment and degree of growth hormone insufficiency.[1-8] Although both dose and frequency of administration have been considered important, the effects of these on growth response have not been adequately investigated.[2 5 9-11] Growth hormone secretion increases with age, stature, and puberty, which suggests that a varying dose will be required to optimise growth.[12-15]

The aim of this study was to investigate the contribution of various parameters of growth as well as dose and frequency of growth hormone administration to its therapeutic effect over the first year of treatment after the administration of biosynthetic methionyl growth hormone (Somatrem).

Methods

Altogether 42 naive prepubertal children who were growth hormone insufficient (31 boys, 11 girls) received Somatrem, (Somatonorm, KabiVitrum) for 12 months between January 1986 and March 1987 (table 1). Growth hormone insufficiency was diagnosed by analysis of growth velocity (height velocity SDS <−0·8) over a minimum period of one year and the growth hormone response to insulin

Table 1 *Pretreatment clinical data Results are mean (SD)*

	No of children	*Age (years)*	*Bone age (years)*	*Height SDS*	*Height for bone age SDS*	*Height velocity SDS*
Group 1*	13	9·6 (2·3)	7·5 (2·3)	−2·2 (0·5)	−0·8 (2·6)	−1·6 (1·2)
Group 2†	21	8·0 (2·5)	6·3 (2·1)	−2·5 (0·7)	−0·9 (1·6)	−1·8 (1·0)
Group 3‡	8	8·5 (3·6)	6·0 (2·6)	−2·7 (1·0)	−0·2 (1·6)	−2·6 (1·4)
Overall	42	8·6 (2·8)	6·6 (2)	−2·4 (0·9)	−0·7 (1·8)	−1·9 (1·2)

Growth hormone given *4 IU three times a week, †2 IU six times a week, and ‡1 IU twice daily six times a week induced hypoglycaemia (0·15 units/kg) (maximum growth hormone concentration <20 mU/l) combined with thyroid releasing hormone (200 µg) and luteinising hormone releasing hormone (100 µg). Four children had multiple pituitary hormone deficiencies and were on appropriate replacement treatment.

The first 30 children were randomly allocated to one of three subcutaneous regimens Group 1 received 4 IU growth hormone three times a week, group 2, 2 IU six times a week, and group 3, 1 IU twice daily six times a week Two children in group 3 transferred to group 1 and one child from group 2 to group 1 during the first month of treatment because of practical difficulties. The remaining 12 children were allocated to group 2.

Anthropometric assessment was made at intervals of three months by the same observer using standard techniques, and bone age was assessed before and at the end of 12 months.[16 17] The growth parameters were defined as standard deviation scores (SDS) as described by Tanner *et al*.[18]

Insulin like growth factor 1 was measured by the method of Baxter *et al*.[19]

Analysis of variance was used to test differences between the mean responses of the three treatment regimens. The results were then analysed using multiple regression analysis using the parameters of table 1, dose/m^2 body surface area/week, and change in height velocity SDS. Significance was taken at the level of $p<0\cdot05$

Results

There was no significant difference between the groups for pretreatment age bone age, height SDS, height for bone age SDS, or height velocity SDS (table 1). All children in the three groups responded to growth hormone replacement with a highly significant change in height velocity SDS (mean (SD) change +5·0 (2·6), $p<0\cdot001$) (fig 1). There was no significant difference in the mean change in height velocity SDS between the groups although there was a positive trend towards the higher frequency regimens (group 1, +3·8 (1·7); group 2, +5·3 (2·6); group 3, +5·9 (2·7). The height gain achieved was not at the expense of inappropriate advance in bone age in any group with a significant improvement in height SDS for bone age occurring in all groups ($p<0\cdot04$)

To determine the contributory factors involved in the first year of growth hormone replacement, the auxological parameters of table 1 and dose of growth hormone/m^2/body surface area/week were analysed by multiple regression analysis. The groups were taken together as analysis of variance showed no significant differences in the response to the three dosage regimens nor in degree of growth hormone insufficiency as defined by the pretreatment height velocity SDS

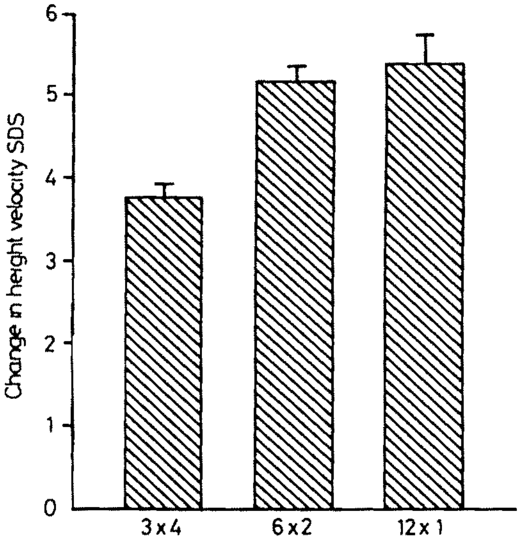

Fig 1 *Response after one year of growth hormone treatment Results are mean (SEM).*

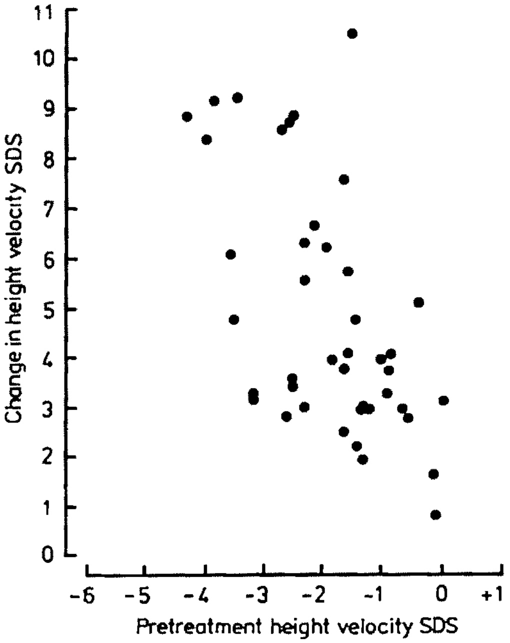

Fig 2 *Change in height velocity SDS in relation to the pretreatment height velocity SDS in 42 children ($r=-0\cdot55$, $p<0\cdot001$)*

Table 2 *Effect of pretreatment height velocity and dose of growth hormone on change in height velocity over one year*

Height velocity SDS (pretreatment)	*<−1*		*−1 to −2*		*<−2*	
	(n=4)	(n=8)	(n=7)	(n=7)	(n=13)	(n=3)
Dose growth hormone/ m^2/week	<15	>15	<15	>15	<15	>15
Change in height velocity SDS (SD)	+2·1 (1·1)	−3·5 (0·8)	+3·6 (1·4)	+4·2 (1·7)	+5·7 (2·5)	+8·5 (1·9)
p Value	<0·002		NS		<0·03	

A highly significant relation between the pretreatment height velocity SDS and change in height velocity SDS (fig 2, $r=0{\cdot}60$, $p<0{\cdot}001$) was expressed by the formula: $y=2{\cdot}22-1{\cdot}28x$. Where y is the change in height velocity SDS and x the pretreatment height velocity SDS. The remaining parameters did not significantly strengthen the relation.

The median weekly dose of growth hormone was 15 IU/m^2/week (range 11–36). An arbitrary cut off at 15 IU/m^2/week was used to examine the influence of dose on the growth response more closely. There was a significant difference between the regression slopes for the pretreatment height velocity SDS and change in height velocity SDS for children receiving more or less than 15 IU growth hormone/m^2/week ($p<0{\cdot}01$). Table 2 shows the effect of receiving more or less than 15 IU/m^2/week within three subdivisions of pretreatment height velocity SDS reflecting differing degrees of growth hormone insufficiency.

Plasma concentrations of insulin like growth factor rose to within the normal range for age in most children during treatment. There was no difference in the concentrations of insulin like growth factor between the three groups either before or after growth hormone and they had no predictive value in determining the growth response to growth hormone.

Discussion

Insufficient growth hormone secretion severely compromises a child's final adult height and there are several reports of the final height achieved after growth hormone replacement.[7,8] Although growth hormone can correct a failing growth rate, the final outcome of treatment cannot be regarded as completely successful because mean final heights achieved have been between −2 and −3·3 SDs from the population mean. At best only 50% of patients attained a final height within 2SD of their target height.[7,8] Close comparison of the studies is difficult due to variation of subjects and different treatment schedules. The results show, however, that final height potential has been irretrievably lost before growth hormone treatment has been instituted, treatment simply preserves what height potential remains but cannot improve it. Thus one would predict that the earlier treatment was introduced and the less the height deficit at that time, the better would be the end result. A growth hormone insufficient child treated from birth would grow normally and we have observed children with congenital hypopituitarism treated with growth hormone from shortly after birth to grow at a normal velocity.

Joss *et al* showed a significant correlation between outcome and the growth velocity in the first year of growth hormone treatment but did not relate the response to the growth hormone regimen employed.[7] The aim of our study was to investigate the factors that may influence the growth response during the first year of growth hormone treatment. This is the first report investigating the contribution of dose, frequency of growth hormone administration, and pretreatment auxological parameters to the therapeutic effect of Somatrem.

All the children showed an improvement in growth velocity in the first year of treatment. The children receiving the higher frequency regimens had the greatest improvement in growth rate, confirming the work of Albertsson-Wikland *et al.*[9,10] Although frequency of administration was an influencing factor in the growth response to growth hormone, the magnitude of response was primarily determined by the pretreatment height velocity SDS and the dose/m^2/week of growth hormone administered. This is in agreement with the study of pituitary growth hormone of Tanner *et al*[1] and would be predicted by the asymptotic relation we have shown between growth hormone secretion and height velocity.[12,15] Our results also show that a dose of at least 15 IU growth hormone/m^2/week is required to optimise the growth response observed. Different patient selection, availability of pretreatment auxological data, varying dose, and the regimens employed in previous studies make comparison of the contribution of dose between studies difficult.[1–8]

The United Kingdom Medical Research Council working party concluded that an acceptable cost benefit ratio in the treatment of growth hormone insufficient children was achieved on a weekly dose of 12 IU human growth hormone in three equally divided intramuscular injections.[5] A standard dose does not take into account the difference in surface area of the developing child or the observation that growth hormone secretion increases with age and pubertal development.[13 14]

These data taken in conjunction with known results of final height after growth hormone treatment strongly emphasise the importance of early diagnosis and therapeutic intervention before long-standing growth hormone insufficiency severely compromises the growth potential of the affected child. Therefore although the intial growth acceleration on growth hormone is less noticeable in the less severely affected child the final outcome will be more satisfactory.

We recommend earlier recognition of growth failure due to growth hormone insufficiency by use of height velocity charts and prompt treatment with growth hormone before height has fallen below the 3rd centile. The dose should be maintained at not less than 15 IU growth hormone/m^2/week throughout childhood and should be administered by equally divided daily subcutaneous injections.

We thank Children Nationwide Medical Research Fund for financial support and Dr D Teale, St Luke's Hospital, Guildford, for measurement of the insulin like growth factor concentrations

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Accepted 27 November 1987

Archives of Disease in Childhood, 1988, **63**, 495–500

Gonadal dysfunction after treatment of intracranial tumours

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SUMMARY Ninety three children (51 boys, 42 girls) who had been treated for brain tumours not affecting the hypothalamopituitary axis, were studied for evidence of gonadal dysfunction. All had received cranial irradiation, 59 spinal irradiation, and 28 adjuvant chemotherapy. Mean age at treatment was 6·3 years (range 1·5–15). Mean follow up after completion of radiotherapy was 8·5 years (range 1–27). Primary ovarian damage occurred in seven out of 11 (64%) girls treated with craniospinal irradiation alone and in nine out of 14 (64%) of those treated with craniospinal irradiation and chemotherapy. The association with spinal irradiation was significant. Primary gonadal damage also occurred in three out of four children treated with chemotherapy combined with cranial irradiation and in three out of nine boys treated with chemotherapy and craniospinal irradiation but in no boy given craniospinal irradiation alone. The only common chemotherapeutic agent was a nitrosurea. Hypogonadotrophic hypogonadism was found in seven boys, 5·8% of children of pubertal age.

Primary gonadal dysfunction is a well known complication of the treatment of some childhood malignancies, particularly leukaemia and lymphoma.[1–8] The prevalence and aetiology of gonadal dysfunction after treatment of brain tumours in childhood are unclear; this is because reported series are relatively small and because of differences in treatment Most authors have attributed gonadal damage to scatter from spinal irradiation[9 10] but more recently Ahmed *et al* concluded that adjuvant chemotherapy was responsible.[11] Brown *et al* also referred to girls with primary ovarian damage after treatment with lomustine (CCNU) without spinal irradiation.[10] Three affected girls with ovarian damage attributed to spinal irradiation, described by Rappaport *et al*, had also received chemotherapy.[9]

Gonadal dysfunction can also be secondary to gonadotrophin deficiency caused by cranial irradiation[9 12] but there are few data on the incidence after the treatment of childhood brain tumours Rappaport *et al* reported that gonadotrophin deficiency may occur infrequently in these patients.[9]

We have studied the aetiology and prevalence of primary and secondary gondal dysfunction in a large cohort of children treated for brain tumours.

Patients and methods

Altogether 125 children who were in clinical remission after receiving radiotherapy for brain tumours not affecting the hypothalamopituitary region were studied. Information about gonadal function is reported for 93 of them (51 boys, 42 girls). The remaining 32 children were still prepubertal with serum gonadotrophin concentrations appropriate for age. They were not included in the analysis because hypogonadotrophic gonadal dysfunction cannot be excluded until they reach puberty.[13] The mean age of the 93 children at treatment was 6·3 years (range 1·5–15) and mean follow up since completion of radiotherapy 8·5 years (range 1–27). Eighty one children were prepubertal when treated, 86 children (48 boys, 38 girls) were of pubertal age when studied The diagnosis was medulloblastoma in 37 children, astrocytoma in 26, glioma in five, ependymoma in 11, pineal germinoma in eight, optic nerve glioma in four, with one ganglioglioma and one meningioma.

After surgery in most children, megavoltage cranial irradiation using either a 5 MeV linear accelerator (n=46) or cobalt 60 source (n=47) was given to a calculated median hypothalamic dose of 47 Gy (40–55) in 34 fractions (range 30–40) over 49 days (range 30–99). Fifty six children also received spinal irradiation using a direct open field to S2–S3 with a median dose of 32 Gy (range 29–33) in 25 fractions (range 20–30) over 43 days (range 30–91). Twenty eight children received adjuvant chemotherapy. The cytotoxic agents given were: intravenous lomustine 340–1200 mg/m^2, vincristine 4–51 mg/m^2, and methotrexate 2–4·5 g/m^2 singly or in different combinations Lomustine and vincristine were generally given according to International Society of Paediatric Oncology (SIOP) schedules.[14]

Primary gonadal dysfunction and gonadotrophin deficiency were identified by clinical assessment of puberty and measurements of basal serum gonadotrophin concentrations and, in most, peak responses to intravenous gonadotrophin releasing hormon 100 µg. Statistical analyses were made by χ^2 and th Mann-Whitney tests.

Results

PRIMARY OVARIAN DYSFUNCTION

Eighteen of 42 girls (43%) had evidence of primar ovarian dysfunction as judged by raised basal serun gonadotrophin concentrations (table 1). There was significant association between craniospinal irradia tion and primary ovarian dysfunction (p<0·01), bu the addition of chemotherapy to craniospinal irra diation did not increase the incidence significantly In girls not given spinal irradiation, however

Table 1 *Incidence of primary gonadal dysfunction according to treatment*

	Ovarian dysfunction		*Testicular dysfunction*	
	Without chemotherapy	*With chemotherapy*	*Without chemotherapy*	*With chemotherap*
Cranial irradiation	0/14	2/3	0/15	1/1
Craniospinal irradiation	7/11	9/14	0/16	3/9

Table 2 *Clinical details of girls with primary ovarian dysfunction (n=18)*

Type of irradiation with or without chemotherapy	*Type of tumour*	*Age treatment given (years)*	*Chemotherapy given*	*Investigations*		
				Age at which undertaken (years)	*Follicle stimulating hormone (IU/l[*])*	
					Basal	*Peak*
Cranial with chemotherapy	Glioma	1·3	Lomustine, vincristine	9	4·4	24
	Astrocytoma	6·0	Lomustine	12	3	50
Craniospinal with chemotherapy	Medulloblastoma	1·3	Lomustine, vincristine, methotrexate	4·6	12	>30
	Medulloblastoma	3·2	Lomustine, vincristine	7·4	20	>40
	Medulloblastoma	4·6	Lomustine, vincristine	8·6	>40	>40
	Ependymoma	5·7	Lomustine, vincristine	8·2	29	61
	Medulloblastoma	6·8	Lomustine, vincristine methotrexate	10	13	>50
	Medulloblastoma	7·1	Lomustine, vincristine methotrexate	8·7	12	38
	Medulloblastoma	8·4	Lomustine, vincristine	11·6	>50	>50
	Medulloblastoma	10	Lomustine, vincristine	12	13	>20
	Ependymoma	2·0	Vincristine	9	7·3	>125
Craniospinal without chemotherapy	Ependymoma	2·0		16	5·8	19
	Medulloblastoma	2·3		6·3	13·5	20
	Medulloblastoma	3·6		5	10·9	20
	Ependymoma	3·7		10·5	40	40
	Medulloblastoma	4·0		4·7	9·2	>50
	Medulloblastoma	8·3		9·1	8	18·9
	Medulloblastoma	10·5		11·8	9·2	17

[*] Normal concentration follicle stimulating hormone basal, <3 IU/l, peak prepubertal, 5·8 IU/l, peak pubertal, 6·21 IU/l

[†] Normal concentration luteinising hormone basal, <3 IU/l, peak prepubertal, 7·1 IU/l, peak pubertal 18·2 IU/l

[‡] B=breast stage development according to Tanner[19]

chemotherapy made a significant contribution to subsequent ovarian dysfunction (p<0·02); lomustine was common to those with ovarian damage. There was no relation between doses. duration, or timing of cytotoxic agents and presence of damage. There was also no relation between the type of radiotherapy source, cobalt 60 or linear accelerator, and the incidence of ovarian damage, although the cobalt 60 source has a wider penumbra. Affected girls were significantly younger at treatment (age 5·7 year *v* 7·0 years) (p<0·05). Transiently raised serum follicle stimulating hormone and luteinising hormone concentrations detected in two prepubertal girls within 0·7 years of completing spinal irradiation had returned to normal within 1·8 years. The pubertal development of affected girls was variable as shown in table 2

PRIMARY TESTICULAR DYSFUNCTION

Four of 44 boys (9%) had raised basal and peak serum follicle stimulating hormone concentrations and two had raised luteinising hormone concentrations. All had received chemotherapy (table 3). The association with chemotherapy was significant (p<0·02), but there were no differences in dose or duration of chemotherapy between them and those unaffected. Two of the four boys made normal pubertal progress but had final testicular volumes of less than 12 ml; sperm counts were not obtained. Puberty arrested in one boy at 14 years and he was treated with testosterone. The fourth boy was of prepubertal age.

It is possible that a boy could have primary testicular dysfunction and be gonadotrophin deficient and the former would not be detected by gonadotrophin concentrations. Boys with gonadotrophin deficiency have therefore been excluded from the analysis of primary testicular dysfunction.

GONADOTROPHIN DEFICIENCY

Delayed (>2 SD) or arrested (>18 months) puberty were rare in the 86 children of pubertal age. There were five affected boys, with low basal and peak serum concentrations of follicle stimulating hormone and low or normal concentrations of luteinising hormone (table 4). Two had pineal tumours, which can interfere with gonadotrophin secretion, suggesting that the true prevalence of treatment

Luteinising hormone (IU/l)†		*Onset of puberty (years)*	*Progress of puberty‡ (age in years)*	*Oestrogen treatment (age in years)*
Basal	*Peak*			
66	99	16	Arrested B2 (17 0)	17·0
6	70	12	Arrested B3 (13 6)	13·6
1	8 2	Prepubertal		
1	29	9	Arrested B3 (13·5)	13 5
33	>100	9	Arrested B3 (11 4)	11 4
34	>100	10 7	Menarche (12·5)	
8 9	>50	Prepubertal		
<1	13	10·9	Arrested B2 (12·2)	12 2
31	>100	13 5	B4 (15·0)	
2 7	>35	11	B3 (12 9)	
11	>100	12	Amenorrhea B5 (17)	
21·6	>40	9	Menarche (11)	
1 5	6	Prepubertal		
1·3	13	Prepubertal		
24	86	10	Arrested B4 (12 5)	12 5
3 8	13·7	Prepubertal		
1 6	6·3	10 3	Arrested B3 (13 1)	
3 2	10	13 1	B4 (14·0)	

Table 3 *Clinical details of boys with primary testicular dysfunction (n=4)*

Type of irradiation	*Type of tumour*	*Age radiotherapy given (years)*	*Chemotherapy given*	*Investigations*
				Age at which undertaken (years)
Cranial	Astrocytoma	4	Lomustine	9
Craniospinal	Medulloblastoma	12·3	Lomustine, vincristine	19
	Medulloblastoma	14	Lomustine, vincristine	29
	Medulloblastoma	5·8	Lomustine, vincristine	11

*Normal concentration follicle stimulating hormone basal, <3 IU/l, peak prepubertal, 5·8 IU/l, peak pubertal, 6·2 IU/l
†Normal concentration luteinising hormone· basal, <3 IU/l, peak prepubertal, 7·1 IU/l, peak pubertal, 18·2 IU/l

Table 4 *Clinical details of boys with gonadotrophin deficiency (n=5)*

Type of tumour	*Age radiotherapy given (years)*	*Radiation dose to hypothalamus (Gy)*	*Investigations*	
			Age at which undertaken (years)	*Pubertal stage**
Medulloblastoma	[illegible]	52	9	1/1/1 2/2
Astrocytoma	14	54	17	2/1/1 4/4
Medulloblastoma	[illegible]	45	12	1/1/1 2/2
Pinealoma	[illegible]	45	17	1/1/1 2/2
Pinealoma	1	48	11	1/1/1 2/2

*Puberty ratings, according to Tanner,[19] given as genitals/pubic hair/axillary hair with testicular volumes in ml

related gonadotrophin deficiency may be even lower. No girl was affected. There was no difference in hypothalamopituitary irradiation between the affected and unaffected children. Two girls had transient amenorrhoea but normal basal and peak serum gonadotrophin concentrations. Of these one had secondary amenorrhoea lasting 13 months and the other, who had been treated at 9 years, reached menarche at the age of 17 years.

Discussion

We have shown that spinal irradiation and chemotherapy may each cause primary gonadal dysfunction separately in a substantial number of children treated for brain tumours remote from the hypothalamus or pituitary. Spinal irradiation was the dominant gonadotoxic treatment. This is shown by the preponderance of ovarian dysfunction when comparing boys and girls treated with spinal irradiation and chemotherapy and the failure of chemotherapy to affect the prevalence of ovarian dysfunction in these girls. The relatively few studies of ovarian function after abdominal or spinal irradiation in childhood show that ovaries are vulnerable to damage at any age.[2 5] Our data support this but show an increased prevalance among younger girls, which may indicate that the ovary is more vulnerable but which is more probably due to the greater mobility of the ovarian position in relation to the spinal field.

Ovarian dysfunction was not a consistent complication of spinal irradiation, as others have shown.[9-11] The likely explanation is provided by serial pelvic ultrasound scans that show that ovaries move frequently, particularly in a lateral plane (J Adams, Middlesex Hospital, personal communication). This observation may have implications for the prevention of ovarian damage, suggesting that only adequate surgical transposition (oophoropexy) will reduce the incidence of radiation induced damage. Oophoropexy has been shown to reduce the incidence of amenorrhoea in adult women after irradiation for Hodgkin's disease.[15] The uncertainty

Follicle stimulating hormone (IU/l)		*Luetinsing hormone (IU/l)*		*Onset of puberty (years)*	*Outcome (testicular volumes in ml)*
Basal	*Peak*	*Basal*	*Peak*		
9·7	20	1·7	20	Prepubertal	
7·8	—	2·5	—	12	Small testes 10/10
>20	—	12·5	—	12	Small testes 10/10
9	13	10	16	11	Arrested 6/6 at 14·6 years

					Pubertal process	
Follicle stimulating hormone (IU/l)		*Luteinising hormone (IU/l)*		*Serum testosterone (nmol/l)*	*Age examined (years)*	*Pubertal stage*
Basal	*Peak*	*Basal*	*Peak*			
<1	<1	<1	2·2	—	12·5	Prepubertal
<1	1	<1	2	—	18	2/1/1 4/4*
1·7	3	1·7	4·6	—	15·5	Prepubertal
1	2·7	7·6	9·6	0·7	17	Prepubertal
<1	<1	4·3	8·8	<0·6	14	Prepubertal

about ovarian position also means that accurate calculations or radiation to the ovaries are not possible. It seems preferable to compare the effects of known radiation doses to the spine.

The gonadotoxic effect of chemotherapy given to children with brain tumours has been recognised in very few studies.[10, 11] Chemotherapy tends to be given in combination with spinal irradiation so data about its independent effect are few. In this study lomustine was the only cytotoxic agent common to children with primary gonadal dysfunction not associated with spinal irradiation. This supports the conclusion of Ahmed *et al*[11] that nitrosureas are gonadotoxic but our data indicate that the effects of spinal irradiation are more important than was suggested in that study. This may be due to the much larger number of children in our series but also possibly to the differences in spinal irradiation techniques used. In the Manchester study of Ahmed *et al*, the spinal radiation beam was directed medially towards the spine while in our patients the beam was perpendicular to the skin. There were no differences in fractionation. If these differences in outcome are substantiated, modifications in radiation technique might be justified.

There is controversy about the sensitivity of prepubertal gonads to damage by chemotherapy[3, 5, 16] and the relative sensitivity of testes and ovaries to damage by chemotherapy or radiotherapy.[17] Few children received chemotherapy alone but the affected girls were prepubertal, and there were equal numbers of affected prepubertal and pubertal boys

Gonadotrophin deficiency not explained by the tumour site was rare at the median follow up of 8·5 years. Hypopituitarism is known to evolve up to 10 years after similar doses of irradiation for pituitary tumours, (40–50 Gy),[18] so ours may be an underestimate. No relation with radiation dose was seen but the dose range was relatively narrow.

This is the largest reported study of gonadal dysfunction in this group of patients and shows that primary gonadal dysfunction was not uncommon particularly after gonadal radiation or certain cytotoxics whereas secondary gonadal dysfunction was rare. Long term endocrine follow up of these children is clearly required of the centres treating them. As survival improves the complications of treatment are found more often and should be considered when devising new treatment regimens.

We thank the Cancer Research Campaign for financial support and Drs HJG Bloom, N Godlee, and J Tobias for access to their records at the Royal Marsden and University College Hospitals and Drs AC Whitton and J Britton for their help

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Accepted 26 November 1987

Archives of Disease in Childhood, 1988, **63,** 501–505

Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty

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SUMMARY Nineteen boys, mean age 14·4 years (range 12·9–16·3), with constitutional delay of growth and puberty were randomised into two groups in a double blind fashion for a three month period. Ten boys received oxandrolone, 2·5 mg per day (mean dose 0·072 mg/kg/day), and nine boys were treated with placebo. Mean growth velocity increased from 4·5 cm/year in the oxandrolone treated group to 9·6 cm/year in three months, and this was sustained at 8·6 cm/year after cessation of treatment. In the placebo treated group, growth rate showed no alteration from 5·1 cm/year to 5·2 cm/year; boys in this group were then treated with oxandrolone, 2·5 mg a day (mean dose 0·073 mg/kg/day) for three months and growth velocity accelerated to 8·6 cm/year. Serum concentrations of insulin-like growth factor -1/somatomedin-C (IGF-1) increased during oxandrolone treatment and continued to rise after treatment had ceased. There was no change in serum IGF-1 concentration during treatment with placebo. Oxandrolone, when used in an appropriate regimen, is an effective, safe treatment for boys with constitutional delay of growth and puberty.

We have previously shown that the anabolic steroids fluoxymesterone[1] and oxandrolone[2] are effective in low dose, three month regimens in the treatment of constitutional delay of growth and puberty in boys. Low dose, short course regimens of these anabolic steroids do not result in the inappropriate advancement of epiphyseal maturation[1 2] that undoubtedly occurs when higher doses are used.[3] There has been criticism, however, that in the low dose regimen used, the increase in growth rate observed might have been due to the onset of the spontaneous growth acceleration of puberty or to a placebo effect.[4] The absence of an appreciable effect on epiphyseal maturation could have made the latter a possibility but Sobel has indicated that the effect of anabolic steroids on epiphyseal maturation is dose dependent whereas the effect on growth is not.[5] We have investigated both possibilities by the use of a double blind placebo controlled trial of oxandrolone.

Patients and methods

Nineteen boys, mean age 14·4 years (range 12·9–16·3), with constitutional delay of growth and puberty were recruited from the growth clinic at The Hospital for Sick Children, Great Ormond Street. All boys had findings consistent with constitutional delay of growth and puberty[6]; all had delayed puberty, height below the third centile for chronological age, and delayed skeletal maturation (mean bone age delay 2·0 'years') All had experienced psychological difficulties associated with their short stature but none had received psychiatric treatment. Approval was obtained from the Standing Committee on Ethical Practice at the hospital and written parental consent obtained. Approval was only granted for three month treatment periods as longer duration of placebo treatment was considered unethical for boys with delayed puberty whose reason for treatment was psychological distress As oxandrolone has no product licence in the United Kingdom approval for this trial was obtained from the Department of Health and Social Security.

The study was double blind, placebo controlled and was conducted in parallel on two groups of boys. At the start of treatment boys were randomly allocated into two groups: group A (n=10) and group B (n=9) Chronological age and bone age delay between the two groups were similar (table). Only one boy from each group had attained stage 3 genitalia; the other boys had genitalia maturation at stage 2. Mean testicular volume was similar in both groups, a mean of 4·9 ml in group A and 4·7 ml in group B. Mean (SD) pretreatment growth velocity was 4·5 (0·8) cm/year in group A and 5·1 (1·7) cm/year in group B which were not significantly different (p>0·1). Boys in group A were treated with one 2·5 mg tablet of oxandrolone/day for a mean of 0·25 years (range 0·21–0·28). Boys in group B received one placebo tablet/day for a mean of 0·27 years (range 0·23–0·41). Boys in both groups were directed to take the tablets during the early evening. For ethical reasons the code was broken after the first three month anthropometric assessment. Boys who had received placebo (group B) were offered oxandrolone 2·5 mg daily for three months, and all accepted. Group A, who had been treated with oxandrolone, received no further treatment during the second three months except for one boy who had no growth response and was given a further three month course of oxandrolone of 2·5 mg/day The mean dose of oxandrolone was 0·072 mg/kg/day (range 0·057–0·097) in group A and 0·073 mg/kg/day (range 0·051 to 0·088) in group B. None of the boys experienced side effects related to oxandrolone treatment.

Stature was measured by standard anthropometric techniques using a stadiometer at intervals of three months [7] Pubertal maturation was assessed by the method described by Tanner.[8] Testicular volume was measured using an orchidometer [9] Venous blood was drawn from all patients at the end of the pretreatment, first, and second treatment periods. Serum IGF-1 concentration was measured by radioimmunoassay after acid-ethanol extraction.[10] Antiserum R557A and [^{125}I]IGF-1[11] were provided by Dr D J Morrell, Institute of Child Health, London. IGF-1 values were expressed as potency relative to pooled normal adult human reference serum defined as 1 unit IGF-1/ml. Intra-assay and interassay coefficients of variation were <8% and <10%, respectively. Statistical analysis was by paired and unpaired *t* tests.

Results

Treatment periods and rates of progression of sexual maturation were identical in both groups. Growth data from groups A and B are shown in fig 1. Growth velocity increased from a mean of 4·5 cm/year to 9·6 cm/year (p<0·001) after three months of oxandrolone treatment (group A) and this was sustained at 8·6 cm/year (p<0·001) after treatment had ceased. One boy did not have a growth acceleration during three months of oxandrolone treatment but did so during a further three months treatment; we do not know if this was due to

Table *Pretreatment clinical data from 19 boys with constitutional delay of growth and puberty*

	Patient No	*Chronological age (years)*	*Bone age delay (years)*	*Genitalia stage*	*Testicular volume (ml)*
Group A	1	13·4	1·0	2	04/04
	2	15·9	1·4	3	08/08
	3	15·0	0·8	2	04/04
	4	13·2	1·3	2	04/04
	5	12·9	2·5	2	05/05
	6	13·7	0·9	2	06/06
	7	13·9	0·6	2	05/05
	8	15·1	4·2	2	05/05
	9	16·3	1·5	2	06/05
	10	13·3	2·6	2	03/03
Mean (range)		14·3 (12·9–16·3)	1·7 (4·2–0·6)		4·9 (3–8)
Group B	1	13·5	3·1	2	05/04
	2	14·1	3·0	2	03/03
	3	13·3	2·4	2	05/04
	4	13·5	0·8	2	04/04
	5	16·2	3·1	2	05/04
	6	14·7	2·6	2	04/04
	7	15·4	1·4	2	06/06
	8	14·2	2·5	3	06/06
	9	15·0	1·8	2	06/06
Mean (range)		14·4 (13·3–16·2)	2·3 (3·1–0·8)		4·7 (3–6)

inadequate duration of treatment, measurement error, or non-compliance. The only boy in group A who had a testicular volume of <4 ml did not have a sustained growth acceleration. We have previously described the attainment of testicular volume of >4 ml as a prerequisite for an oxandrolone induced, sustained growth spurt.[2] The group who received placebo (group B) had no significant change in growth velocity; a mean of 5·1 cm/year increased to 5·2 cm/year ($p>0.5$) after three months. Subsequent treatment of group B with oxandrolone resulted in growth acceleration to a mean of 8·6 cm/year ($p<0.001$)

Serum IGF-1 concentrations are shown in fig 2. In group A, mean serum IGF-1 concentration increased from a mean of 1·01 U/ml to 1·23 U/ml ($p<0.05$) during oxandrolone treatment and further increased to 1·49 U/ml ($p<0.01$) during the post-treatment period In group B there was no significant change in serum IGF-1 from a mean of 0·90 U/ml to 0·88 U/ml ($p>0.5$) on placebo, although there was an increase to 1·33 U/ml ($p<0.01$) after oxandrolone treatment

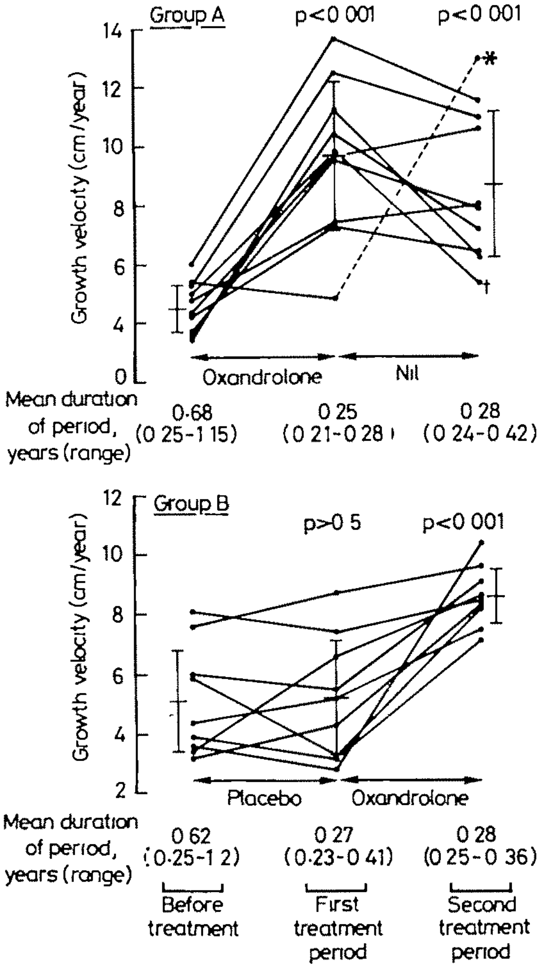

Fig 1 *Growth velocity in groups A (n=10) and B (n=9) during pretreatment, first, and second treatment periods Mean duration of each period (range) are given. The horizontal bars represent the mean (SD). One boy (*) in group A did not respond to oxandrolone in the first three months and received a further three months course (broken line) One boy (†) had a testicular volume of <4 ml.*

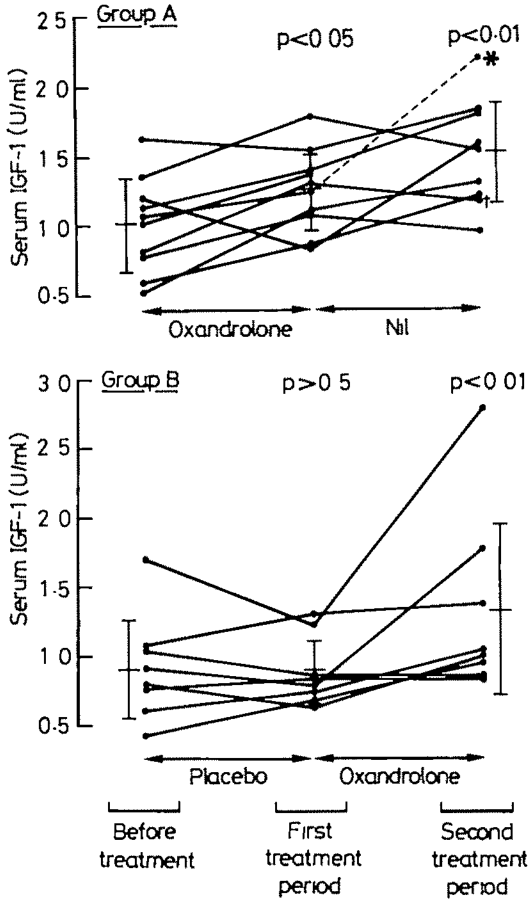

Fig 2 *Serum IGF-I concentration in groups A and B during pretreatment, first, and second treatment periods The horizontal bars represent the mean (SD) One boy (*) in group A did not respond to oxandrolone in the first three months and received a further three month course (broken line) One boy (†) had a testicular volume of <4 ml*

Discussion

We have shown in this study that oxandrolone produced a growth acceleration in boys with constitutional delay of growth and puberty that was sustained in the post-treatment period. This was not a placebo effect. The level of attainment of sexual maturation was insufficient to cause the spontaneous growth acceleration of puberty and consequently the growth acceleration achieved was due to oxandrolone. Indeed, this sustained growth acceleration becomes indistinguishable from the spontaneous growth spurt of puberty[12] at the attainment of stage 3 to 4 genitalia[13] or 10 ml testicular volume.[14] Low dose oxandrolone advanced the timing of the growth spurt with little, or no, interference in the rate of progress of sexual maturation. Certainly there was no clinical evidence of suppression of the hypothalamo-pituitary-gonadal axis (reduction in testicular volume) which has been associated with the administration of larger doses of anabolic steroids.[15]

We believe that oxandrolone, used in the regimen we have described, is an effective and safe treatment for constitutional delay of growth and puberty in boys. None of the boys experienced side effects due to oxandrolone treatment. As the growth response to anabolic steroids is not dose dependent,[5] lower doses than we have used in this study may be as effective.[16] Other potential treatment modalities for constitutional delay of growth and puberty, such as depot testosterone or biosynthetic human growth hormone, may not be as effective as oxandrolone. The former may produce inappropriate advancement of epiphyseal maturation, the latter is very expensive; both have to be given by injection.

We have previously hypothesised that the sustained growth acceleration induced by oxandrolone is caused by a sustained increase in growth hormone secretion.[2] Anabolic steroids increase the growth hormone response to insulin induced hypoglycaemia[17] and the growth hormone response to growth hormone releasing factor.[18] Our serum IGF-1 data point to increased growth hormone secretion induced by oxandrolone and this would explain the sustained pattern of the growth acceleration. This is in addition to a direct action on the tissues which is probably the predominant effect of oxandrolone in prepubertal children.

The response to oxandrolone, in the dose regimen used, was neither due to a placebo effect nor due to the spontaneous growth acceleration of puberty. Anabolic steroids originally came into disrepute because they were used in high dose, long duration courses which suppress the hypothalamo-pituitary-gonadal axis[15] and produce inappropriate bone age advance[3]; such high doses of oxandrolone induce puberty. We have shown that in low dose, short duration courses a sustained growth spurt is induced without virilisation. We believe oxandrolone is a useful treatment for boys with constitutional delay of growth and puberty when psychological problems associated with short stature predominate and when final height prognosis is towards the lower limit of normal; circumstances where it is imperative that no loss of height potential results from treatment. In view of the extensive experience with oxandrolone in North America, and more recently in the United Kingdom, we believe it would be of value if such a useful therapeutic modality were to be licenced for prescription in the United Kingdom.

We are grateful to Miss H Elliston, group chief pharmacist and to Mrs S Patey, principal pharmacist, The Hospital for Sick Children, Great Ormond Street, for their help with this study

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Accepted 18 November 1987

Archives of Disease in Childhood, 1988, **63**, 506–511

Diagnosis and treatment of hysterical conversion reactions

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SUMMARY Twenty children with hysterical conversion reactions were reviewed. The ways in which they became ill, the attitudes of their families to their illnesses and their underlying personal problems were noted. Treatment comprised avoiding unnecessary investigations and removing symptoms by using graded exercises given by physiotherapists. Exploration of the underlying psychological problems took place at a pace with which the family could cope because many families were reluctant at first to accept that the illness was psychological.

Seventeen of the 20 children recovered completely within three months of starting treatment. The results show that early diagnosis and close liaison between paediatricians, physiotherapists, and child psychiatrists are necessary if prolonged handicap is to be avoided.

Hysterical conversion reactions are not common in the United Kingdom[1] being diagnosed in between 0·5–1% of referrals to a child psychiatric inpatient centre[2 3] and 1% of referrals to adult neurological units.[4] The prevalence in paediatric practice is not known. When they do arise, however, they present serious problems of management for the clinician who is anxious about missing organic disease[5 6] but aware of the danger of prolonging the children's disabilities by unnecessary investigations.[7] Many families with such children seem to be resistant to the possibility that a psychological problem exists and clumsy interventions may only result in the families seeking other opinions—events that may cause the clinicians to agree with the families that further tests may be necessary.

The studies of Goodyer,[2] Caplan,[3] and Rock[8] defined the condition precisely: 'prominent somatic symptoms with a disturbance of the central nervous system or of limb dysfunction whose investigation by a specialist unit has failed to establish any anatomical or physiological basis for the complaint'. All three authors stressed the need to make a psychiatric diagnosis. Making such a diagnosis, however, is not always easy given the resistance of some children and their families to intervention by a psychiatrist. Children may fear the loss of the sick role and may go to extreme lengths to persuade their parents and their doctors that they are ill.

The concepts of the 'sick role' and illness behaviour have been helpful in our reappraisal of hysterical conversion reactions and conversion reactions are now treated as different from hysterical personalities and hypochondria, or Briquet's syndrome, described by Kendall.[9] Taylor argued that for a hysterical reaction to develop, the patient had to be in a predicament from which all other avenues were blocked, and that the patient had an ally who helped to promote the sickness, this was either a member of the family or the doctor.[10] Furthermore the patient was usually copying someone (whether current or historical) and hysteria had to be enacted by a person with sufficient social skills. Hence it does not occur in very young children.

Psychological intervention must begin by searching for the importance the illness has for the children, and what they hope to gain by remaining ill;[11] this underlying motivation may or may not be conscious.

Patients and methods

Twenty six children with hysterical conversion disorder[12] seen consecutively in the department of child psychiatry during a three and a half year period in 1983–7 were studied. Six children who had presented with pseudo fits were excluded from the study because their behaviour was episodic and required a different treatment regimen. The remaining 20 children had all been examined and investigated in units specialising in neurology, paediatrics, or orthopaedics, to which they had presented with functional disorders of the central nervous system for which no organic cause could be found.

Psychiatric evaluation of the children included enquiries about recent stresses at home, at school, and with their friends, and possible reasons for remaining ill. Many of the case notes gave verbatim comments on the children's attitudes to life

The aims of treatment and assessment were: to stop further physical investigations and explain the reasons for this in conjunction with the referring specialist and if possible the family doctor; to show that complete recovery was possible with the help of 'face saving' treatment given by a skilled and understanding physiotherapist; and to move towards psychological treatment at a pace which the children and families could accept.[7]

Results

Thirteen girls and seven boys (a ratio of about 2·1) with a mean age of 13 (range 11–15) were diagnosed as having hysterical conversion disorders during the period late 1983–early 1987, nearly 2% of the total number of children seen (n=1090).

PRESENTING SYMPTOMS

Table I shows the symptoms with which the children presented, weakness of the legs accompanied by a bizarre gait being the most common. This often meant that the children clung desparately to someone else or moved with great difficulty with crutches The abnormality of gait was not suggestive of organic disease

Table 1 *Presenting complaints of 20 children with hysterical conversion reactions*

Disability	*No of girls*	*No of boys*	*Total*
Weakness of legs and bizarre gait	5	5	10
Inability to move	2	1	3
Foot drop	2	1	3
Weakness of arm	2	–	2
Contracture of toes	1	–	1
Torticollis	1	–	1
Total	13	7	20

Three children were almost totally incapacitated, one could not bear to sit or stand, and one was apparently so disabled he had to be fed by his mother Another was confined to a wheel chair, unable to feed herself or go to the toilet without assistance The child with torticollis had had her neck in the same position for a year and the child with contracture of the toes had maintained the same position for seven months, though the foot relaxed when she was asleep. Nearly all the children complained of pain in the affected areas. Few of the children behaved as if they were concerned about their symptoms, although their parents certainly were.

DURATION OF SYMPTOMS BEFORE REFERRAL TO A PSYCHIATRIST

Twelve of the children had had their symptoms for over three months and five for more than a year Only two had had symptoms for less than a month (table 2). Most had considerably reduced their activities often entailing time off school and disruption of family life. All the children had been seen by specialists, none had been referred directly to the child psychiatrist by the family doctor or school medical officer. Thirteen were referred by paediatric neurologists, four by paediatricians, and three by orthopaedic surgeons.

Only four children had seen a single specialist, eight children had seen two specialists, and four had seen three specialists. Three children, all of whom had had symptoms for over a year, had seen four specialists (usually seeking private opinions).

ATTITUDE TO THE CHILD'S ILLNESS

A pronounced feature was the anger of many of the families about what they saw as the failure of the medical profession to diagnose or to treat their

Table 2 *Outcome of treatment in 20 children with hysterical conversion reactions*

Duration of symptoms	*No of patients*	*Time taken to recover function*		
		<1 Month	*>1 Month but <3 months*	*>3 Months*
<1 Month	2	2	0	0
>1 Month but <3 months	6	3	3	0
>3 Months but <6 months	6	5	1	0
>6 Months but <1 year	1	0	0	1 (partial)
>1 Year	5	3	0	2
Total	20	13	4	3

child's illness properly Table 3 gives examples of statements made by the parents about the doctors they had seen in the past. The reasons for this hostility often lay in the families' previous history but they could have also been enhanced by insensitive or inadequate handling of the initial complaint.

ASSOCIATED ORGANIC DISEASE

Most of the children had had a minor illness or accident at the onset of their symptoms though it was not always easy to assess the importance of this in retrospect. Physical trauma was given as the reason for the onset of the symptoms by seven children, and a viral illness by four. Two children had associated osteochondritis but this was not thought to be responsible for their symptoms.

There was someone for the child to copy in at least seven of the families—for example, one girl who progressed from backache to total immobility had a grandfather who had been operated on for a slipped disc. Another girl presented with weakness of the legs, and her father had back pain for which he felt he had not been treated satisfactorily.

PARENTAL PSYCHIATRIC ILLNESS

The parents of five of the children had had psychiatric illnesses in the past that had been of sufficient severity to have been temporarily incapacitated, and two of them had seen a psychiatrist. Three parents had had anxiety states and one father was having psychiatric treatment for endogenous depression at the time of his daughter's referral. Two of the mothers had suffered from agoraphobia.

Table 3 *Twelve typical examples of parents' reactions*

Mother “ felt that fractured toe was not *x* rayed soon enough ”

Parents. “ . felt plaster put on in casualty did not fit Previous dissatisfaction with hospital treatment when child was a baby ”

Father “Almost every medical opinion we have had has proved to be wrong ”

Parents. “They treated us as if we were stupid ” Parents had sought different opinions—mainly privately

Mother “They gave me to understand she might have had a brain haemorrhage ” Mother lacked confidence in medical opinion

Father Wanted to sue school for negligence about injury at hockey

Mother Would not believe doctors' opinion that there was no organic disease Previous cot death

Parents “No-one told us osteochondritis was self-limiting! We had too many different opinions ”

Grandfather who had had disc surgery felt no-one outside S---- Royal Infirmary was any good.

General practitioner prescribed penicillin “He should know he is allergic to it ”

“His TB test was positive, they started him on tablets ” False result

Parents. Very dissatisfied with initial treatment. “They did not *x* ray his knee ”

It was not possible to ascertain more precisely how anxious the parents were at the time of referral though the mothers' anxious behaviour was often commented on, especially by nursing staff

HISTORY OF PREVIOUS ‘PSYCHOSOMATIC ILLNESS’ IN CHILDREN

Five girls and one boy had previous histories of non-specific aches and pains which were thought to have been of psychological origin.

More strikingly, six of the seven boys and eight of the 13 girls had no such history and their parents thought they would be unlikely to make a fuss about illness or to have psychological problems, hence their difficulty in accepting the psychological nature of the presenting complaint. None of the children had ever been referred to a child psychiatrist or child guidance clinic previously.

PSYCHIATRIC ASSESSMENT OF THE CHILD

Psychiatric assessment of the children was not always easy because of the resistance of either the children or the families, or both, to the idea of the problem being psychological. They were also concerned about the stigma of being referred to a psychiatrist. It was essential for the referring specialist to explain to each family why referral to a psychiatrist was important, and it was for this reason that we usually saw the most severe cases, as well as those who had already been admitted, on the paediatric ward, for the first consultation.

Parents and child were usually seen separately though family interviews sometimes formed part of the treatment. Though ‘saving face’ was part of the treatment, we felt it was both unwise and dishonest to disguise the identity of the psychiatrist. The children were told that sometimes worries and problems of which they may or may not have been aware, played tricks on the body and stopped it getting better as quickly as it should. Our job as child psychiatrists was to find out if they might have any such problems.

Our aim was to win the confidence of each child gradually, and to counsel nursing staff and parents that an attitude in which the child was accused of ‘putting it on’ would increase resistance to treatment. Occasionally a play therapist treated the child.

Usually the children together with their parents began to discuss areas of difficulty during a series of interviews and for the sake of simplicity these are divided into the following three categories: (1)

problems within the family—that is problems of parental disharmony, sexual abuse, or feeling ignored by preoccupied parents; (ii) problems concerned with peer groups—that is feeling bullied and intimidated, or feeling friendless, and (iii) problems concerned with school work—that is feeling unable to cope, working too hard, or having specific reading or spelling difficulties, or both. Five children had serious problems in more than one category.

Problems within the family

Families were considered 'disharmonious' when the parents freely admitted to stress that resulted in an atmosphere of tension and mutual recrimination that could be sensed by the children. Four families came into this category. One girl whose parents were separated was afraid of her father's violence when he came to take her out. Of the two girls who eventually admitted that they were being sexually abused, one had been abused by her 28 year old brother who was still living with the family and the other had been abused by a close friend of her father's. Neither had sufficient evidence of physical abuse to convict the offenders, nor had they felt able to confide in their parents. One boy felt his parents were too preoccupied to attend to his needs.

Problems concerned with peer groups

Four of the seven boys and four of the 13 girls admitted to problems concerned with their peer groups. The boys were concerned about bullying and issues of sexual identity whereas the girls usually complained of losing friends or feeling excluded from the group because they felt different—for example, being too tall, too fat, or having the wrong accent.

Table 4 *Statements about educational pressures made by or about children*

Patient "I'm not clever, I can't really cope" IQ 100 Child attending independent grammar school with high academic standards

Patient. 'Daddy won't mind as long as I'm above average " Father late university entrant

Mother "She sets very high standards for herself " She had typed solidly for three days

Mother "She presses herself, she wants to be top "

Patient. "I feel guilty if I don't get everything right "

Mother "She's a perfectionist."

Patient "I can never catch up " (Academically or physically) Family described themselves as fitness fanatics, child had osteochondritis.

Patient "I worry about getting everything right "

Mother: said child had specific reading difficulties but will not admit it Plays truant

Brother "He has to be top in everything and be first in all his races "

Mother "He works seven hours a night, he wants to be a doctor to please his grandmother " Child had specific reading difficulties

Problems concerning school

Ten of the 20 children felt under pressure to achieve or push themselves unnecessarily. As academic pressure is a subjective thing, and as many of the children were achieving a great deal, statements made by them or by their parents are listed in table 4.

Most of the children seemed remarkably unconcerned about the importance of their symptoms—that is whether they were going to get better or not, but four children had moderate to severe anxiety states, two had mixed disorders of anxiety and depression, and three became clinically depressed, albeit for brief periods, after the diagnosis had been made Two of these were the girls who had been sexually abused. Indifference was not therefore a totally reliable feature.

TREATMENT

Treatment was aimed at moving the emphasis from the physical to the psychological aspect of the illness at a pace with which the family could cope. For those children who had already seen several specialists, a further stay in the paediatric ward was often recommended after the child psychiatrist had become involved. This was partly to give time for the family to develop confidence in the psychiatric team and partly (with the aid of the physiotherapists) to show that the children were recovering. We suggested to some of the children that it would not be right for them to go home before they were completely better. This was an effective technique if we could be sure that the child, though reluctant to stop faking illness, was even more reluctant to remain in hospital indefinitely. Weekend leaves were allowed as long as progress was being made in physiotherapy.

Three children were admitted to the psychiatric unit and some of the children treated on the paediatric ward attended the psychiatric unit day school Six children were treated as outpatients. Psychological treatment depended on the problem underlying the symptom but was usually mainly supportive, occasionally bringing in the whole family.

OUTCOME

Thirteen of the 20 children recovered from their physical symptoms within one month of the start of treatment, and 17 had recovered within three months. Of the three who took longer all were girls and all had had their symptoms for more than six months. They had all begun with minor trauma and not viral illnesses. Two recovered completely during the next 12 months. The girl with contracture of the toes still had some flexion deformity at the time of writing, but she had no contractures and could wear ordinary shoes. She was mildly handicapped.

Two families withdrew from treatment before the psychological problems had been fully addressed, and two were referred to child psychiatric services nearer their homes, but failed to proceed with treatment At the time of writing the children had had no recurrence of their physical symptoms. One girl who alleged that she had been sexually abused by her 28 year old brother recovered from her physical symptoms and went to live with her sister under the supervision of the social services department. At the age of 17 (when her brother had gone to live abroad) she returned home and later that year was knocked down by a car and killed.

Discussion

Hysterical conversion disorders, though puzzling to the clinician and a challenge to the psychiatrist, are quite rare. The group studied represented about 2% of all referrals to the child psychiatric department at a hospital that takes referrals to the neurological department from the whole region. It is similar to other studies in the strict diagnostic criteria used, including those children who were treated as outpatients. The ratio of girls to boys of 2:1 was as expected[2 3].

Treatment was similar to that advocated by Dubowitz and Hersov[7] but occasionally we used a paradoxical technique of recommending treatment in hospital in selected cases until the children had recovered. We felt that this gave the physiotherapist a more effective part in encouraging them to get better. It also showed the parents that the children were improving, and helped us to gain their trust.

One of the greatest difficulties for the psychiatrist when asked to see these children was to decide whether there was a psychiatric disorder, and this difficulty was made worse when there was resistance and sometimes active hostility from the parents, and when the child denied that there were problems. Though most of the children were eventually found to have difficulties in their lives, these were not always obvious at the first interview.[13]

An important observation in this series is that no child was under the age of 11 years. This supports Taylor's observation that children must have the necessary social skills to fake illness and the diagnosis should therefore rarely be considered in very young children.[3 10]

Taylor also proposed that in children sickness is promoted by an 'ally' who may be a member of the family who continues to believe that the child is physically ill despite evidence to the contrary, or it may be the doctor who continues to investigate unnecessarily. It was apparent in the group studied that several of the families were angry at what they saw as the incompetence or inadequacy of their doctors, and this often had its roots in the family's past experience. This attitude itself may force doctors to investigate and even operate against their better judgment, and in three cases comments were made to that effect by consultants. General practitioners should be in a position to advise families not to go from specialist to specialist and have the condition investigated over and over again, but with some of these families this would have been hard to resist.

The children's problems started in different ways. Many of them had had minor illnesses or accidents from which they failed to recover. Without these it is possible that some of them may not have developed the reactions at all but others may have expressed their distress in different ways. Conversely, the degree of apparent disability did not readily relate to the severity of the problems the children were experiencing. It may be that the combination of several factors was necessary to produce the reaction, namely the initial experience of feeling unwell, a personal predicament that was difficult to talk about but that may or may not have been serious, the social skill to fake the illness, and the attitude of the families towards the children's conditions. The response of the doctors could then be contributory. Once the children had stated they were ill it could have been difficult to escape without loss of face.

The problems that the children had were those of children with emotional disorders—that is, anxieties about school, friendships, and their parents.[3] Only one of the children had any behaviour problem and he had played truant from school because of reading difficulties; he was described as sensitive and anxious. An interesting finding, however, was the extreme conscientiousness not to say perfectionism of at least half of the children, and it was this characteristic which could have led paediatricians to agree with the families that such exemplary children who were doing so well academically and socially and who had had no previous psychiatric histories could not possibly have had psychiatric problems. Academic stress has been noted previously as an underlying problem in childhood hysteria.[14] Moreover it is these children who may be unable to admit that they have any problems. Sexual abuse is of course another predicament that is often difficult to talk about.

The follow up has been concentrated on the children's physical recovery, but confirms other studies.[2 7] More detailed psychiatric follow up is, however, necessary, particularly in the longer term.

This report highlights the benefit of a vigorous, multidisciplinary therapeutic programme which takes into account the parents' anxieties, the children's need for a 'face saving' escape, and an opportunity to discuss emotionally charged issues in a way that was not possible hitherto.

I thank Dr Elena Garralda for permission to report four of her patients and for her helpful comments in the presentation of this paper, and Miss Sue Almond, senior physiotherapist, for her invaluable assistance

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Accepted 7 December 1987

Archives of Disease in Childhood, 1988, **63**, 512–517

Home intravenous antibiotic treatment in cystic fibrosis

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SUMMARY The prognosis for patients with cystic fibrosis who are colonised with *Pseudomonas aeruginosa* has improved as a result of the regular use of intravenous antibiotics; however, this necessitates long periods of hospitalisation. Home intravenous antibiotic treatment has potential advantages over hospital treatment. We describe our experience during the first 20 months of using a system of home intravenous antibiotic treatment in which a cystic fibrosis liaison sister has an essential role. Thirteen patients have received 40 courses of treatment. There were highly significant improvements in weight, respiratory function, and white cell count during home treatment. There was no significant difference in weight and forced expiratory volume in one second between the end of home treatment and the end of hospital treatment while forced vital capacity was better after home treatment. All patients preferred home treatment. The advantages of home visits by the cystic fibrosis liaison sister during treatment are emphasised.

The prognosis for patients with cystic fibrosis who are colonised or infected with *Pseudomonas aeruginosa* has improved over recent years as a result of the regular use of intravenous antibiotics[1] but this has necessitated long periods of hospitalisation for some patients. Inpatient treatment is disruptive and stressful even when mothers are resident.[2] There are also financial strains, particularly when the patient is under the care of a specialist regional unit, which may be some distance from the patient's home.[3] The need for regular intravenous treatment often starts during the second decade of life when time spent away from school or work may have a particularly deleterious effect on the individual's prospects for future employment. After several admissions most patients and parents became familiar with many aspects of intravenous drug administration and see no reason why they should not do it themselves.

Patients with cystic fibrosis requiring intravenous treatment are often not acutely ill but place a great strain on the accommodation, manpower, and financial resources of the hospital. Drugs may be given late by tired senior house officers who have never had any formal training in the administration of intravenous drugs. There is increasing concern about the possible dangers of cross infection of resistant strains of pseudomonas in hospitals,[4] and there is increasing evidence that viral infections (which are usually rife in paediatric wards) can lead to pulmonary deterioration in patients with cystic fibrosis.[5]

Treatment with intravenous antibiotics at home has been seen by both the patients and the medical profession as a way of avoiding some of the problems outlined above[6]; however, there are several potential problems with home treatment.[6] Intensive physiotherapy and dietetic help are important adjuncts to antibiotic treatment and these will be limited when the patient is at home. Monitoring of the patients' progress with a view to altering treatment is also limited. Some patients require such frequent resiting of their cannulas that it would be pointless to attempt home treatment. It is evident that patients or parents must be capable of learning to give intravenous drugs safely. Patients with cystic fibrosis are routinely expected to take responsibility for much of their management and they may find further responsibilities more stressful than being admitted to hospital. The end results of treatment at home should not be inferior to inpatient treatment.

In February 1986 we introduced a system of home intravenous antibiotic treatment for patients under the care of the Leeds Regional Cystic Fibrosis Unit based at St James's University Hospital in which an essential role is played by a specially trained cystic fibrosis liaison sister. We present our experience and results with this system after 20 months.

Methods

PATIENT SELECTION

The following criteria were considered before training for home intravenous treatment was offered:

1. The patient should have had at least one course of intravenous treatment in hospital. This admission may be used to train the patient and family and assess ease of venous access.
2. The patient and family should be considered to be compliant with other forms of treatment.
3. Intravenous access should be reliable enough to ensure several days of treatment without the need for revision.
4. The home must have been visited by the cystic fibrosis liaison sister to establish that there are suitable areas for safe storage of equipment and a clean area to prepare drugs.
5. The family practitioner should have no objection to home treatment starting.
6. The ability of the family to cope with current levels of stress and responsibility is informally assessed and previous home visits by the liaison sister or social worker are particularly helpful in relation to this.
7. The family should have a telephone in the home.

INTRAVENOUS ACCESS

Intravenous access must be reliable. We used one of the following methods:

1. *Intermittent injection.* Some patients have prominent and easily punctured antecubital veins and preferred to insert a 23 gauge butterfly needle (Venisystems) each time drugs were given. This method allowed great freedom of activity between drug administration.
2. *Cannula.* An ordinary paediatric intravenous cannula was inserted in the forearm where movement was least likely to occur. A 20 cm extension allowed the patient to hold the injection bung easily in one hand while injecting with the other. A lock containing 10 units of heparin/ml (Hepsal, CP Pharmaceuticals) maintained patency between drug administration. Cannules that failed could be replaced at the patient's home by the liaison sister.
3. *Neonatal long line.* A 30 cm fine Silastic neonatal central venous line (Epicutaneo catheter, Vygon) was inserted into a antecubital vein and patency maintained by a lock containing 100 units of heparin/ml (Hep-Flush, Edwin Burgess) as described by Tyrell *et al* (J Tyrell, S Wynn, J Hiller. Experience with neonatal 'long lines' for antibiotic therapy in cystic fibrosis. Abstract to be published in *Scandinavian Journal of Gastroenterology.)* This system usually gave prolonged venous access and had the advantage over other long lines of being inserted through a small (19 gauge) needle and allowing great mobility.
4. *Totally implantable intravenous access devices (Port-A-Cath, Pharmacia)* In patients with poor venous access who were going to need repeated courses of intravenous treatment this system allowed guaranteed access with a single skin puncture.[7] The 90° Huber point needle and short extension were changed every seven days.

TRAINING

The liaison sister trained parents and patients who were mature enough to learn to check, reconstitute, and dilute drugs as well as draw up and give them by slow bolus injection Depending on the type of intravenous access being used instructions were also given on flushing the line, inserting a heparin lock, using butterfly needles, and managing a Port-A-Cath. A syringe pump was used for drugs that had to be infused over a long period. Care was taken to ensure that patients were aware of the signs of local problems with intravenous access and systemic drug reactions.

Patients and parents usually quickly acquired considerable skill and knowledge in all aspects of intravenous drug administration during inpatient treatment. Final instruction was given during the administration of the first dose of the first course of home intravenous treatment. The patient or parent gave the second dose of drugs under close observation. A member of staff confirmed on the home record of intravenous treatment that the patient/parent was competent in both theory and practice; if they were found to be incompetent intravenous treatment at home had to be delayed. Written instructions were given to each family.

STARTING TREATMENT

All first doses were given in hospital and the patient was observed for 30 minutes after this and asked to stay in the hospital for a further 90 minutes. If a drug was used that the patient has not had before then the second dose was also given in hospital and observation continued for 30 minutes after this.

The time spent in hospital was used to examine the patient and check baseline weight and to perform respiratory function tests and haematological investigations.

The patient left the hospital with all the equipment and drugs for the first week of treatment (the family practitioner prescribed drugs for subsequent weeks' treatment), a container for 'sharps,' a peak expiratory flow meter, and record chart. They also had the home telephone numbers of the liaison sister and a member of the medical staff of the unit.

MONITORING

Blood for monitoring of aminoglycoside concentrations was collected by the liaison sister on the second or third day of treatment.

The patient kept a twice daily record of his peak expiratory flow and the liaison sister visited at least once a week (more often during the first course of treatment) to review progress by assessing the patient's general condition degree of cough, and sputum volume and colour. Respiratory function could also be checked by a portable spirometer (Vitalograph-Compact, Vitalograph). Failure to improve led to a review of treatment. If compliance seemed poor or the family seemed to be having difficulty coping action was taken to correct this or terminate the home treatment.

Results

Forty courses totalling 596 days of home intravenous antibiotic treatment were given to 13 patients (eight girls, five boys) aged 9 to 28 years. Patients lived up to 80 miles from the hospital. At the start of the first course of home treatment Shwachman scores ranged from 50 to 90 (mean 72) and Chrispin Norman *x* ray scores from 6 to 26 (mean 12). One patient received eight courses of treatment.

P aeruginosa was the main pathogen at the start of 38 courses. In one course *Haemophilus influenzae* and in another course *Staphylococcus aureus* and *H influenzae* were isolated at the start of treatment but in both instances *P aeruginosa* had been isolated from the previous culture The following antibiotics were used (number of courses of treatment). tobramycin (25), ceftazidime (22), azlocillin (12), amikacin (9), aztreonam (4), ticarcillin (4), and piperacillin (1). Venous access was by cannula in 15 courses, Port-A-Cath in 12, intermittant injection in 11, and neonatal long line in six. Cannulas lasted between two and 13 days (mean four days) and neonatal long lines between four and 17 days (mean nine days)

Courses of home treatment lasted from seven to 36 days (mean 15) and in 15 courses there was some associated inpatient treatment lasting from two to 18 days (mean six days). Reasons for associated inpatient treatment are shown in the table. Drug reactions were encountered in five courses In two cases patients complained of generalised aches and tiredness that resolved within 24 hours of stopping azlocillin. Two patients had a mild rash and were admitted for change of treatment while one patient developed an urticarial rash within minutes of receiving intravenous tobramycin and ceftazidime at home. This patient was admitted, and subsequent challenge with ceftazidime precipitated an anaphylactoid reaction requiring intravenous chlorpheniramine and hydrocortisone.

There were highly significant improvements in weight ($n=34$, $p<0.0003$), peak expiratory flow ($n=38$, $p<0.0001$), forced expiratory volume in one second ($n=34$, $p<0.0001$), forced vital capacity ($n=34$, $p<0.0001$), and white cell count ($n=20$, $p=0.009$) during home intravenous treatment (fig 1). There was symptomatic improvement during all courses of treatment except for the four indicated in fig 1 by symbols: in course 1 the patient had very advanced disease and died within two months of treatment. In course 2 the patient was admitted because of failure to improve adequately and did not start to improve until a week later. In course 3 the patient showed a deterioration in respiratory function that was not in keeping with his otherwise very good response to treatment. In course 4 there was clinical improvement but chest radiography showed signs of allergic bronchopulmonary aspergillosis and there was a rise in IgE. Steroid treatment produced a further improvement of respiratory function and clearing of the radiograph.

Weight, forced expiratory volume in one second, and forced vital capacity were compared at the end of the most recent course of hospital treatment with the end of the course of home intravenous treatment closest to it (fig 2). All three of these parameters

Table *Inpatient treatment associated with home intravenous treatment (n=15)*

	No of courses	*Reason*
Inpatient treatment before outpatient treatment	6	For initial stabilisation
	2	Previous drug reaction
	1	Post partum (24 year old)
	1	Insertion of Port-A-Cath
Inpatient treatment between outpatient treatment	1	Chest pains
Inpatient treatment after outpatient treatment	3	Drug reactions
	1	Failure to improve at home

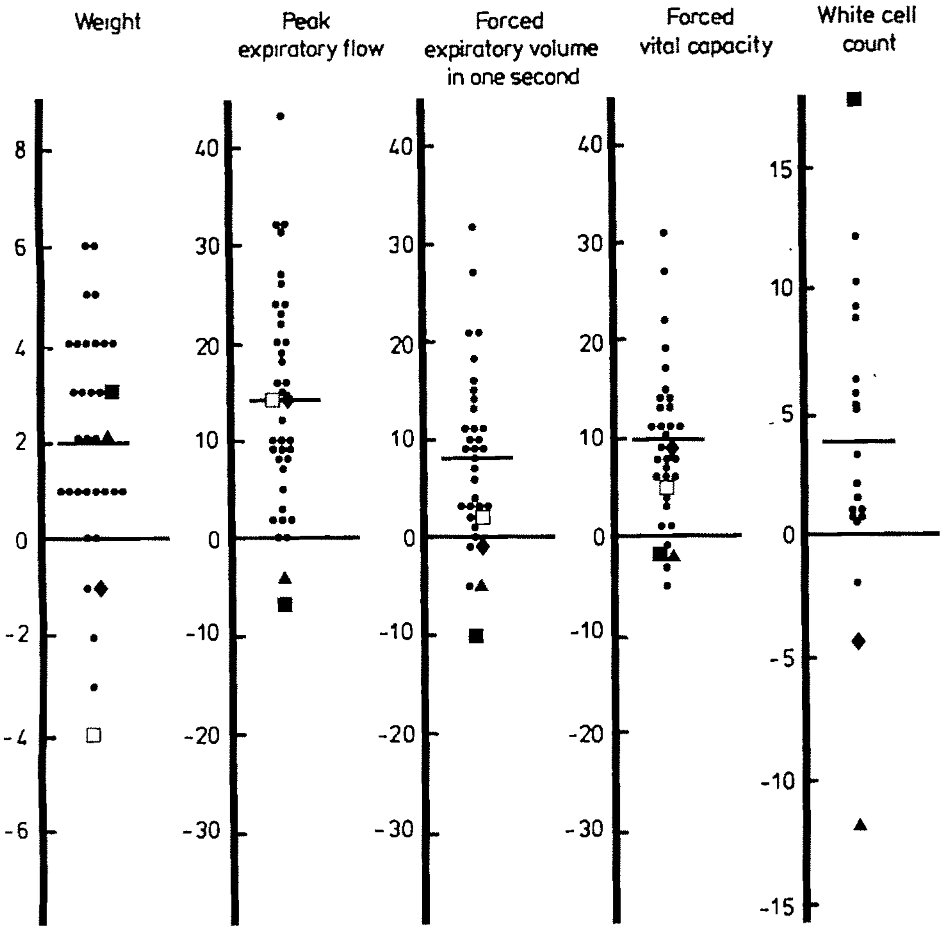

Fig 1 *Changes during home intravenous treatment Weight is expressed as change in percentage predicted weight for height Peak expiratory flow, forced expiratory volume in one second, and forced vital capacity are expressed as changes in percentage predicted White cell count is expressed as the fall in the number of white cells* $\times 10^9/l$*—that is, a negative result indicates a rise in white cell count. Course 1 (▲), course 2 (□); course 3 (■), course 4 (◆)*

were better after home treatment than after hospital treatment and this reached significance for forced vital capacity (weight (n=11), not significant; forced expiratory volume in one second (n=10), not significant, and forced vital capacity (n=10), p=0·025).

One patient had not had any previous inpatient treatment but he and his mother were exceedingly distressed by the prospect of admission because his sister had died of leukaemia on the paediatric ward at this hospital a few years earlier.

One patient was refused further use of the service after the discovery of a 1 year old child playing with vials of heparin when the liaison sister visited.

Another patient (results not included) received prolonged intravenous treatment at home during the terminal phase of her disease and both she and her parents found this preferable to hospital admission or withdrawal of antipseudomonal antibiotics The sibling of this patient subsequently needed intravenous treatment and the parents felt able to cope with this at home, however, an early visit by the liaison sister showed a high level of stress and the remainder of the treatment was given in hospital.

No one has yet rejected the idea of home treatment when it has been offered. One family have been unable to start home treatment because of unsuitable housing conditions. Several families have asked about home intravenous treatment but have been temporarily refused because of poor venous access

The reaction of families to home and hospital

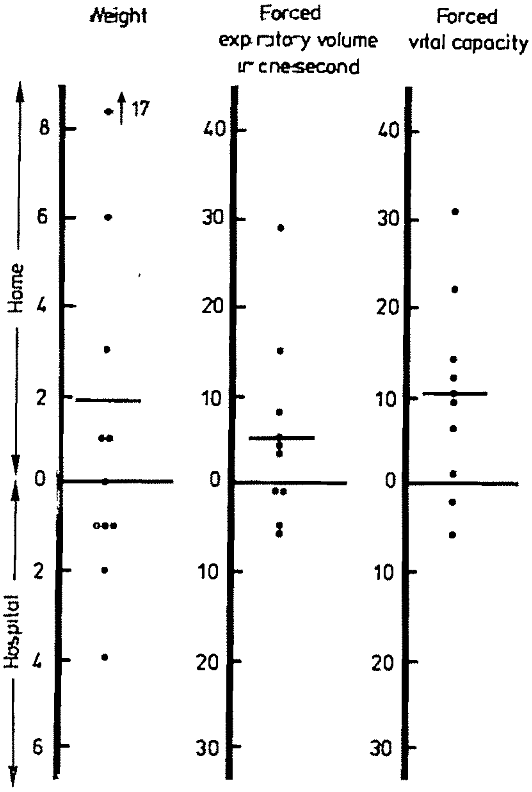

Fig 2 *Comparison of weight and respiratory function after home and hospital intravenous treatment. Weight for height and percentage of predicted forced expiratory volume in one second and forced vital capacity expressed as difference after hospital and home treatment—that is, those below the zero line were better after hospital treatment*

treatment were canvassed using a postal questionnaire which included a visual analogue scale to assess the stress of inpatient and outpatient treatment. All families preferred home treatment. Reasons for preferring home treatment included better food, more facilities to exercise, better sleep patterns, better timing of drug administration, and less interruption of education and career. The advantages of hospital treatment were considered to be more effective physiotherapy and the reassurance of having medical help at hand. During home treatment eight patients attended work or school for more than 50% of the time and most families found financial advantages (of up to £110 per week) because of reduced travelling expenses to hospital and because earnings were not lost. All families felt some degree of stress during home treatment but only two considered this greater than the stress of a hospital admission (and even these patients preferred to continue with home treatment).

On the basis of the cost of inpatient accommodation alone (£81·37 per day) the home intravenous service is saving £29 098 a year at this hospital

Discussion

Our system of managing home intravenous treatment for patients with cystic fibrosis has been safe, has proved successful in improving the patients' condition, and does not seem to be inferior to inpatient treatment.

Systems of managing outpatient intravenous antibiotic treatment have been advocated before[8–10] but it is often undertaken on an informal ad hoc basis. Although there have been no reports of serious problems, there are inherent dangers with home intravenous treatment[6] and a single serious accident may bring the whole practice into disrepute. Careful patient selection and training together with good venous access and observation when the first dose is given (that is, when the patient is at greatest risk of serious drug reaction)[11] help to ensure safety. The time needed for training varies. It is wise to record in the notes that training has been completed and the person giving the drugs understands the dangers and is competent to give them.[12] Our experience has convinced us that one of the most important contributions to safety and effectiveness is the provision of a member of the team who can regularly monitor progress, compliance, and stress in the home. Easy communications with members of the team are also vital, particularly if there are any signs of drug reactions or problems with intravenous access. These aspects of our system have allowed us to safely manage five incidents of drug reaction as well as pick up poor compliance, progress, and ability to cope. This has allowed us to make appropriate changes in management. The regular home visits and frequent communications with the family also have an important supportive role.

This study shows that home treatment is not without stress, but despite this most patients find it less stressful and prefer it to inpatient treatment.

Some parents may find home intravenous treatment unacceptably stressful and when this happens the child may see their parents' refusal to continue as an act of rejection. In this case it is important that the responsibility for a change to hospital treatment is taken by the caring team and not the parents.

We believe that home based intravenous treatment using the system we have described will become an attractive alternative to hospital treatment for many patients as more of them come under the care of units with large catchment areas and the staff and expertise to ensure effective implementation of such schemes.

We thank the Cystic Fibrosis Research Trust for funding Dr J Gilbert, the Cystic Fibrosis Research Fellow, and the Joseph Levy Charitable Foundation for funding Sister Teresa Robinson, the Cystic Fibrosis Liaison Sister

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Accepted 19 January 1988

Archives of Disease in Childhood, 1988, **63,** 518–521

Uptake of immunisations in low birthweight infants

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SUMMARY The timing of immunisations for preterm infants is controversial. Because of the statement by the British Paediatric Association/Joint Committee on Vaccination and Immunisation Liaison group that immunisations should normally begin three months after the date of birth, the records of all infants born in 1984 and currently (June 1986) resident in the London Borough of Newham were studied to find out if this recommendation was being implemented. Subjects were divided into groups by birth weight and where possible by gestational age. Cumulative uptakes by age of any component of the first and third triple immunisations, and of the pertussis component, were plotted separately. Comparison of uptake of the first course showed a considerable initial delay for infants weighing less than 2000 g at birth compared with heavier babies, but by 18 months the coverage was almost identical. This difference was not evident for the third course. A similar delay was apparent when infants of 37 weeks' gestation or less were compared with babies born at full term, though recording of gestational age was incomplete. Final overall uptake was poor for all groups. Differences among groups in numbers consenting were not an important factor.

Informing those responsible for giving the immunisations of these findings has stimulated their interest in improving practice by implementing the recommendations.

The London Borough of Newham is a deprived urban borough with a multiracial population. The proportion of children in the population is high and movement in and out of the borough is considerable. The overall uptake of immunisations in Newham is low, but of particular concern is that babies of low birth weight or short gestation may be especially poorly protected.

The age at which preterm infants should begin their primary course of immunisations is controversial[1] but the current recommendation endorsed by the British Paediatric Association/Joint Committee on Vaccination and Immunisation Liaison Group is that immunisation of these infants should normally begin three months after their date of birth.[2] This regimen is likely to produce an acceptable immune response without increasing the risk of adverse reaction.[3]

We have compared the uptake of immunisations for babies of low birth weight and for preterm infants with that of their peers of normal birth weight. In view of the particular concern about pertussis immunisation and the vulnerability of small infants (especially during the recent epidemic), uptake of the pertussis antigen was studied separately as were other components of the triple immunisation.

Methods

Data on all infants born in 1984 and currently (June 1986) resident in Newham were studied. The regional child health computer register provided the most complete and accurate data on immunisations available,[4] including those given to infants before they moved to the borough. These data were used to produce graphs of uptake by age using SASGRAPH and infants were subdivided into groups by birth weight and by gestation.

Data for birth weight were complete, and accurate to within 10 g. A limit of 2000 g was used to separate low birthweight infants (n=395) from normal (n=3426) infants, as in 1984 this was the weight below which an infant would automatically be admitted to the special care baby unit—an event that leads to a baby being labelled as 'different' from other infants.

Data for gestation were only available for 3502 infants. Omission was more likely for low birthweight infants, 313 of 395 low birthweight infants and six of 3426 normal birthweight infants having no record of length of gestation (table 1). Comparisons were first made between infants born at full term (38 or more completed weeks' gestation), preterm infants (32–37 completed weeks' gestation) and very preterm infant (31 completed weeks' gestation or less); numbers in the last group, however, were too small to permit informative comparisons.

Other factors which might have influenced uptake were studied. The most obvious of these was ethnic origin[5] but recording of this was so inaccurate that analysis could not be performed.

The frequency of consent for immunisations and whether or not this consent included pertussis was also studied. Immunisation was discussed with the family by the health visitor shortly after birth and a consent form signed if the parents were willing to have the child immunised. The intention to include or exclude any particular antigen was shown on this form. This intention was recorded in the computer file but a further consent was required at the time of immunisation. The frequency with which consent was initially given for immunisation, with and without pertussis, was determined for each birthweight group, and compared with the actual number of immunisations given.

Table 1 *Gestational ages and birth weights of groups studied*

Gestational age (weeks)	*No (%) in low birthweight group*	*No (%) in normal birthweight group*
<31	22 (6)	1 (0·03)
32–37	52 (13)	352 (10)
>38	8 (2)	3067 (90)
Not recorded	313 (79)	6 (0·18)
Total	395 (100)	3426 (100)

Results

When uptake was compared by birth weight, the eventual uptake of the first course with or without pertussis vaccination was similar (fig 1), being 71% for low birthweight infants and 72% for normal birthweight infants for any antigen, 58% for low birthweight infants and 59% for normal birthweight infants for pertussis, but the immunisations were significantly delayed for the low birthweight

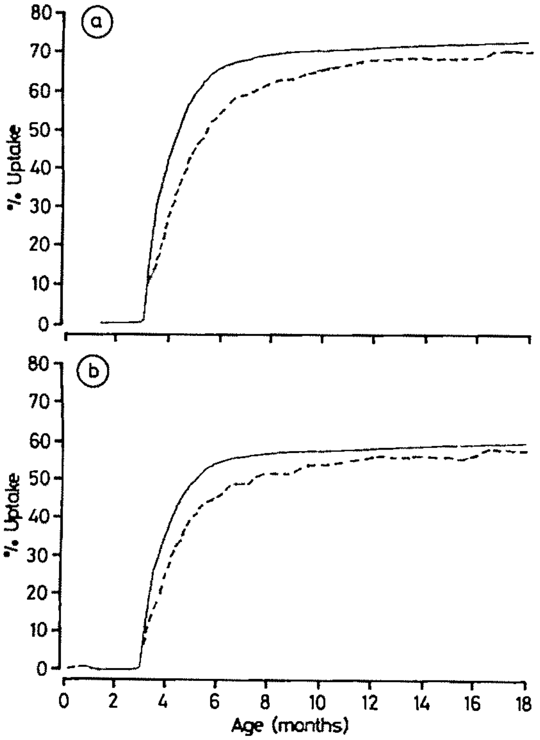

Fig 1 *Eventual uptake by birth weight of first course of vaccination (a) for any antigen and (b) for pertussis alone. Solid lines indicate normal infants and broken lines low birthweight infants*

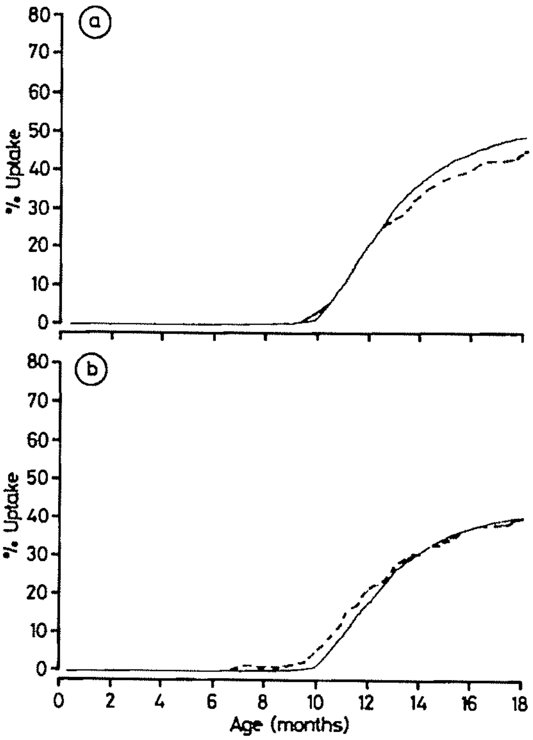

Fig 2 *Eventual uptake by birth weight of third course of vaccination (a) for any antigen and (b) for pertussis alone. Solid lines indicate normal infants and broken lines low birthweight infants*

infants. The percentage of infants receiving any injection within one month of the recommended starting age of 3 months was low—30% for low birthweight infants and 41% for normal birthweight infants.

There was no difference between the two groups in the timing of the third course (fig 2). Rather than indicating a 'catch up' by the low birthweight infants this was because the normal birthweight infants received their third dose later than was recommended, only 11% of each group were immunised within one month of the suggested age of 10 months.

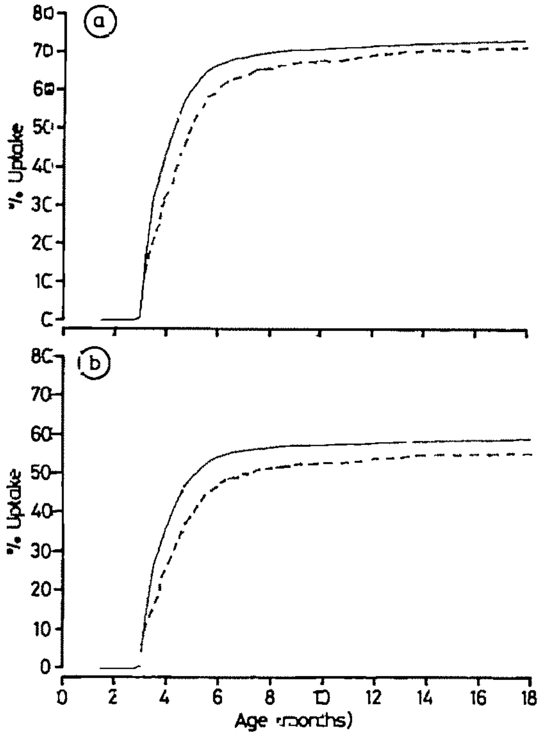

Fig 3 *Uptake by gestational age of first course of vaccination (a) for any antigen and (b) for pertussis alone. Solid lines indicate normal infants and broken lines low birthweight infants.*

When uptake was compared for gestation of age a similar picture emerged (fig 3); 31% of preterm infants and 41% of those born at full term started their immunisations within one month of the recommended age. Eventual uptake for pertussis seemed to be less for preterm infants (56% compared with 60%), but analysis by birth weight (including only those for whom gestational age was known) showed a similar difference suggesting that this discrepancy may have arisen from incomplete recording of data.

Overall rates of consenting to immunisation were similar in both birthweight groups (table 2), and a similar proportion of each subsequently failed to be immunised.

Discussion

The results confirmed the suspicion that the smallest and therefore most vulnerable infants were not being protected as well as possible. Protection of young infants against pertussis by prenatal transfer of maternal antibody is not adequate; the only means of protecting infants is by active immunisation. Pertussis is a distressing illness at any age, but if the baby is small and immature, it is more likely to develop serious complications, and possibly die. In an area in which many older children are not immunised and the potential pool of infection is therefore large (especially during an epidemic such as occurred recently) young infants are particularly at risk, and probably remain so until the second dose of pertussis immunisation has been given.[3] In order to minimise this risk it is wise to begin immunisations as soon as they are both effective and safe.

The similar rates of consent and eventual uptake

Table 2 *Numbers consenting to and receiving immunisations in two groups studied*

	No (%) in low birthweight group (n=395)	*No (%) in normal birthweight group (n=3426)*
Babies with consent to receive immunisation	386 (98)	3350 (98)
Those with such consent who received immunisation	279 (72)	2477 (74)
Those with such consent whose immunisation included pertussis	227 (59)	2046 (61)
Babies with consent to receive pertussis antigen	339 (86)	2898 (85)
Those with such consent who received any other immunisation	232 (68)	2113 (73)
Those with such consent who received pertussis antigen	222 (65)	1985 (69)
Babies with consent to receive immunisation excluding pertussis	47 (12)	452 (13)
Those with such consent who received any other immunisation	45 (96)	364 (81)
Those with such consent who received pertussis antigen	5 (11)	61 (14)

for both birthweight groups suggest that the problems of delivery are not related to concern about contraindications to immunisation as such, but to inappropriate worries about immunising infants below a certain gestational age or weight. This cannot be confirmed by this study, but anecdotal evidence from parents is common.

In order to improve coverage, particular emphasis is now being laid on the recommendation that all infants should begin their immunisations at 3 months of age. Senior community medical officers and senior community nurses are being told this, and in addition there is a written recommendation in the summary that is sent to the general practitioner and to the community clinic for every baby discharged from the special care baby unit. Information is included about the presence or absence of specific contraindications to receiving the pertussis antigen that have arisen in the neonatal period. The subject is also discussed with the parents by staff in the special care units to ensure that their choices are made in the light of current recommendations.

This effort is already meeting with some success; in future we intend to perform similar analyses for infants born in later years to measure this success.

We thank the staff of the North East Thames regional computer centre and the University of London computer centre for their help and advice

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Accepted 21 September 1987

Archives of Disease in Childhood, 1988, **63,** 522–527

Clinical factors associated with retinopathy of prematurity

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SUMMARY In the period from September 1983 until June 1986 a prospective study was carried out to determine the incidence and severity of retinopathy of prematurity in inborn infants of less than 1500 g at birth and the risk factors associated with the development of retinopathy of prematurity in infants of less than 31 weeks' gestation. One hundred and forty four infants were eligible for inclusion in the study. Altogether 140 infants of less than 1500 g birth weight were examined 42 (30%) of whom developed retinopathy of prematurity. Fifteen of these infants had progression to advanced disease (stage III or stage IV).

One hundred and seventeen of the infants were of less than 31 weeks' gestation and 34 (29%) of them developed retinopathy of prematurity. Thirty four risk factors shown previously to be associated with the development of the disease were collected prospectively and analysed using multiple logistic regression analysis to determine the independently significant variables. Three risk factors: acidosis, the number of times that the pH was $<7{\cdot}2$; hyperoxia, the number of times that arterial oxygen tension was greater than 12 kPa; and gestational age were found to be independently associated with the development of retinopathy of prematurity in these infants. These findings suggest that acidosis may be an important aetiological factor in the pathogenesis of this disease.

There is a considerable variation in the reported incidence of retinopathy of prematurity[1–6] and the association of risk factors with its development.[7–25] The most important factor contributing to this variability is likely to be differences in ophthalmic practice in infants in different centres. Thus the selection of infants for examination, the timing of the first retinal examination, and the frequency of follow up examinations will each affect the apparent incidence of the disease. Furthermore the inclusion of retrospective data, and the methods used for statistical treatment of these data may also have important effects. Lastly, differing survival rates of extremely low birthweight infants would be expected to have a profound effect on the observed incidence of retinopathy of prematurity.

The present study was designed to determine the incidence and severity of retinopathy of prematurity in all infants born at less than 31 weeks' gestation or less than 1500 g birth weight and to investigate the association between a range of clinical features and the development of retinopathy of prematurity. Only infants born at the Hammersmith Hospital were included in the study so that risk factors were recorded prospectively by a single observer over a continuous 31 month period and non-uniformity in neonatal care was minimised. Infants were examined early and frequently until term. In all infants less than 31 weeks' gestation, 34 risk factors were recorded prospectively and subjected to multiple logistic regression analysis in order to determine which variables were independently associated with the development and progression of retinopathy of maturity in these infants.

Methods

During the period December 1983 to June 1986, 144 infants of less than 31 weeks' gestation or of less than 1500 g were born at Hammersmith Hospital and survived until at least 2–3 weeks of age. Altogether 140 infants were of less than 1500 g birth weight and 117 infants were less than 31 weeks' gestational age. Ophthalmic examination was first performed at 2–3 weeks of age and at weekly intervals thereafter until discharge from the neonatal unit. A final examination was required at about term. Ventilator or incubator care did not preclude examination, which was performed by indirect ophthalmoscopy with a 28 dioptre lens through dilated pupils. Mydriasis was achieved by the application of phenylephrine 2·5% and cyclopentolate 1% eyedrops at one hour and 30 minutes before the procedure Scleral indentation was only used in selected cases. Neither the ophthalmologist performing the retinal examinations nor the research fellow were involved in the clinical care of the infants. Retinal changes were recorded in accordance with the International Classification Scheme,[26] determining the extent of the developing vasculature affected—that is, stage I. the presence of a demarcation line; stage II· ridge formation; stage III: the presence of a ridge with extraretinal fibrovascular proliferation; stage IV. retinal detachment and the disease location on the retina zones I–III, zone I being the innermost zone with its centre at the optic disc. The stages (I–IV) and retinal location zones (I–III) were recorded separately for each eye at every examination. Retinal changes before the development of the demarcation line were documented but not classified as retinopathy of prematurity. Infants were not discharged until the retinal changes had entered the regression phase in order that the end stage of the disease was known in each case.

Thirty four variables considered to be possible risk factors were recorded prospectively in infants born at less than 31 weeks' gestation by a paediatric research fellow attached to the neonatal unit These variables are summarised in tables 1 and 2 As certain monitoring and diagnostic procedures are likely to vary between hospitals our methods for assessing those variables where there is no agreed standard are described.

INTRAVENTRICULAR HAEMORRHAGE

All infants had cranial ultrasound scans (ATL Mark III mech sector scanner) performed daily in the first week of life and twice weekly thereafter until discharge from the neonatal unit. Intraventricular

Table 1 *Clinical features that differed significantly between infants with and without retinopathy of prematurity (median values or percentage of total)*

Feature	*Infants with retinopathy of prematurity (n=34)*	*Infants without retinopathy of prematurity (n=83)*	*p Value*
Birth weight (g)	870	1080	<0·002
Gestational age (weeks)	27	29	<0·00001
No (%) with intraventricular haemorrhage			
Grade 1	7 (21)	9 (11)	<0·01
Grade 2	17 (50)	16 (19)	
Grade 3	3 (9)	4 (5)	
No having top up transfusion	6	1	<0·0001
No having exchange transfusion	0	0	<0·05
No (%) with sepsis			
Suspected	9 (26)	43 (52)	<0·01
Confirmed	21 (62)	15 (18)	
Duration of ventilation (days)	10	1	<0·00001
Duration of oxygen treatment (days)	49	4	<0·00001
No of episodes PO_2 >12 kPa	13	2	<0·00001
Duration of PO_2 >12 kPa (hours)	9	7	<0·00001
No of episodes PCO_2 >8 kPa	12	0	<0·00001
Duration of PCO_2 >8 kPa (hours)	56	0	<0·0001
No (%) with patent ductus arterious (treatment required)			<0·001
Fluid restriction	8 (24)	5 (6)	
Indomethacin	14 (41)	21 (25)	
Surgery	1 (3)	0	
No of episodes PO_2 <5·3 kPa	2	0	<0·005
Duration of PO_2 <5·3 kPa (hours)	9·4	0	<0·002
No of episodes PCO_2 <3 kPa	1	0	<0·05
No of episodes pH <7·2	11	0	<0·00001
Duration of pH <7·2 (hours)	24	0	<0·00001
No of episodes pH <7·1	0	1	<0·05
Duration of pH <7·1 (hours)	0·75	0	<0·05
Duration of parenteral nutrition (days)	19	5	<0·00001
No (%) with apnoea (treatment required)			<0·005
Spontaneously reverting	10 (30)	34 (41)	
Stimulation only	13 (38)	21 (25)	
Bagging with 40–100% FiO_2	11 (32)	5 (6)	

Table 2 *Risk factors that did not differ significantly between infants with and without retinopathy of prematurity*

Factor	*Score/Range*
Fetal growth retardation	0–1
Maternal pre-eclampsia	0–1
Maternal diabetes	0–1
Maternal smoking	0–1
Antepartum haemorrhage	0–1
Ruptured membranes	0–2
>24 hours	1
+Amnionitis	2
Apgar score (at 5 minutes)	0–10
Small for gestational age	0–2
Weight <10th centile	1
Occipito-frontal circumference <10th centile	2
Ventricular dilatation	0–1
No of days parenteral nutrition	0–100
Pneumothorax	
PCO_2 <3·3 kPa (hours)	
PCO_2 >8 kPa+PO_2 >12 kPa (episodes)	

haemorrhage was graded I to III in accordance with the classification of Levene *et al.*[29]

PATENT DUCTUS ARTERIOSUS

The presence of appreciable patent ductus arteriosus was determined on clinical grounds with or without the help of cardiac ultrasonography if an infant had bounding pulses and the appropriate murmur with or without cardiac failure. Patent ductus arteriosus was graded 0–3 as follows. (1) The duct closed spontaneously with or without fluid restriction. (2) The duct closed only after indomethacin treatment. (3) Surgical closure was necessary

OXYGEN MONITORING

All infants receiving supplemented oxygen treatment had continuous monitoring either of arterial oxygen tension by means of an umbilical artery oxygen electrode (Biomedical Sensors) or via a transcutaneous electrode (Radiometer TCM1); this was calibrated regularly by arterial blood gas sampling. Thus the number and duration of episodes during which the $PtCO_2$ or PaO_2 was greater than 12 kPa or less than 5·3 kPa was determined.

CARBON DIOXIDE (PACO2) AND PH MONITORING

The number of episodes during which the $PaCO_2$ was greater than 8 kPa or less than 3·3 kPa or the pH was less than 7·2 or less than 7·10 was determined from intermittent arterial blood gas sampling. Because the sicker babies were likely to have more frequent blood gas sampling an estimated maximum time during which infants were acidotic or hypercarbic, or both, was calculated as the sum of the intervals between the abnormal samples and the previous samples for either pH or $PaCO_2$.

APNOEA

Apnoea was defined as a cessation of respiration for >20 seconds and was scored 1–4. A score of 1 was allocated if the apnoeic episodes were spontaneously reverting, 2 if stimulation was required, 3 if bagging with 40–100% oxygen was required, and 4 if ventilation was required for reversion.

SEPSIS

Sepsis was suspected and a score of 1 allocated if an infant had an abnormal immature to total white cell ratio and was neutropenic or neutrophilic with (a) an unstable temperature, (b) frequent bradycardias, or (c) poor peripheral perfusion A score of 2 was only allocated if these criteria were met in the presence of a positive bacterial culture.

RISK FACTOR EXPOSURE

Risk factor exposure during the period from birth until the appearance of a demarcation line (stage I) in those infants developing retinopathy of prematurity was compared with exposure to the same factors in unaffected infants in the period from birth until before their discharge from the neonatal unit. In addition those infants who developed only stage I or stage II retinopathy of prematurity were compared with those who progressed to developed advanced disease (stage III and IV). In order to identify risk factors that could be associated with progression from mild (stage I and II) to severe (stage III and IV) disease, risk factors were compared both in the period up till the appearance of a demarcation line and again from this point until regression or progression to stage III or IV was observed.

ANALYSIS

Statistical analysis was achieved by means of the χ^2 or unpaired Student's *t* test to determine the dependent variables associated with the development of retinopathy of prematurity Stepwise logistic regression analysis was used to determine the independent variables associated with the development of retinopathy of prematurity and its progression to advanced disease (stage III–IV)

Results

Retinopathy of prematurity was observed in 34 out of 117 (29%) infants born at less than 31 weeks' gestation (mean (SD) gestational age 28 (1·5) weeks), and in 42 out of 140 (30%) infants of birthweight less than 1500 g (mean (SD) birth weight 1100 (240) g).

Table 3 *No of infants with different stages of acute retinopathy of prematurity in relation to birth weight*

Birth weight (g)	*Without retinopathy of prematurity*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
500–750	2		2		3
751–1000	27	7	10	5	2
1001–1250	42	2	4	1	1
1251–1500	27	1	1	3	
Total	98	10	17	9	6

The patients were classified according to the most advanced end stage in either eye

The mean (SD) age at diagnosis was 7·4 (3) weeks, the mean (SD) postconceptual age at diagnosis was 34·8 (2·7) weeks. All new cases were diagnosed between 30 and 40 weeks' postconceptual age. Of the 42 low birthweight infants developing retinopathy of prematurity 30 had a normal retinal examination when first seen. The age at diagnosis seemed to be later in the less mature infants but there was no significant correlation between age at diagnosis and postconceptual age.

The severity of the retinopathy was inversely proportional to both birth weight and gestational age (tables 3–6) In no case was unilateral retinal disease observed, but in seven cases asymmetrical disease was seen. Four of the seven progressed to stage IV in one eye and stage III in the second eye, in three of these infants non-progression to stage IV may have been influenced by cryosurgical intervention. Two infants had stage III retinopathy of prematurity in one eye and stage II in the second, while a single infant had stage II disease in one eye and stage I in the second.

Table 4 *No of infants with different zonal disease of retinopathy of prematurity in relation to birth weight*

Birth weight (g)	*Without retinopathy of prematurity*	*Zone III*	*Zone II*	*Zone I*
500–750	2	2	1	2
751–1000	27	7	17	
1001–1250	42	4	4	
1250–1500	27	2	3	
Total	98	15	25	2

All but two infants had a similar zonal distribution in the two eyes; these two infants had zone III disease in one eye and zone II disease in the second.

Two infants had retinal detachments in both eyes (one zone I and one zone II), and four infants had unilateral retinal detachments. Bilateral blindness resulted in two cases and unilateral blindness in another three. The sixth infant developed a unilateral retinal detachment, but this did not affect the macula and visual development during the first two years of life was normal.

Regression of retinopathy of prematurity was observed in all cases. Infants with stage I and II disease showed complete regression, while those with more advanced retinal changes were left with variable degrees of residual scarring

For 22 of the 34 clinical variables analysed there was a significant difference between these infants who did and those who did not develop retinopathy of prematurity on χ^2 or unpaired t testing (table 1). With stepwise logistic regression analysis, however, only three variables were found to be independently associated with the development of retinopathy of prematurity. These were (a) acidosis—that is, the number of episodes that the pH $<7{\cdot}2$ ($p<0{\cdot}001$); (b) gestational age ($p<0{\cdot}05$); and (c) the number of episodes when $\mathrm{PaO_2} >12$ kPa ($p<0{\cdot}05$).

Similarly, acidosis ($p<0{\cdot}001$), $\mathrm{PaO_2} >12$ kPa ($p<0{\cdot}001$) and the occurrence of pneumothorax

Table 5 *No of infants with different stages of acute retinopathy of prematurity in relation to gestational age*

Gestational age (weeks)	*Without retinopathy of prematurity*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
24–26	3	4	3	4	2
27–28	37	3	10	3	2
29–30	43	2	1		
Total	83	9	14	7	4

The patients were classified according to the most advanced end stage in either eye.

Table 6 *No of infants with different zonal disease of retinopathy of prematurity in relation to gestational age*

Gestational age (weeks)	*Without retinopathy of prematurity*	*Zone III*	*Zone II*	*Zone I*
24–26	3	4	8	1
27–28	37	6	12	0
29–30	43	2	1	0
Total	83	12	21	1

($p<0·05$) in the period before the appearance of a demarcation line were all independently significantly associated with the development of advanced disease (stage III and IV) By contrast after the appearance of a demarcation line, there was no difference in exposure to any of the 34 risk factors between those infants with mild (stage I and II) disease and those with advanced (stage III and IV) disease.

Discussion

Estimates of the incidence of retinopathy of prematurity[1–7] range from 3–5%[6] to 39%.[7] In the present study the observed incidence of the disease in infants less than 1500 g birth weight of 30% is in agreement with most previous studies. It is unlikely that the disparity in reported incidence from different units reflects a true population difference, but is instead likely to be influenced by a number of methodological factors. As both the mortality rate and the incidence of retinopathy of prematurity increase with decreasing gestational age it is important to know both the survival rate and the proportion of extremely low birthweight infants making up the study population in order to compare studies from different units. The survival rate of 85% of all infants of less than 1500 g birth weight within the study period in this unit is higher than that reported in previous studies by Kalina and Karr (59%),[4] Campbell *et al* (69%),[1] Gunn *et al* (60·5%),[3] and Yu *et al* (72%).[5] Altogether 41% of the infants in this study were of less than 1000 g birth weight; this comprises a considerably higher percentage of extremely low birthweight infants than in previous studies [2 5] The survival rate for these extremely low birthweight infants of 65% is also higher than survival rates reported previously.[2 5]

The apparent incidence will also be influenced by the protocol used for retina examination. In the present study, all infants fulfilling the predetermined criteria for inclusion in the study were examined in identical manner. If infants had been preselected and only those determined to be at risk of developing retinopathy of prematurity due to, for instance, oxygen exposure had been examined, or if a large proportion of the infants had been transferred out of the neonatal unit before examination (thus excluding a proportion of the larger babies with fewer neonatal complications) then it is possible that the apparent incidence would have been higher than the true incidence. Flynn has reported a similar incidence as ourselves yet only 57% of infants of birth weight less than 1500 g who survived were examined.[2] The timing of the first eye examination and the frequency of subsequent examinations may also be important. Thirty of the 42 infants who developed retinopathy of prematurity in this study did not have retinal changes on initial examination, and there was also a trend for the less mature infants to develop the disease later. By performing the first examination at 2–3 weeks of age, and then at weekly intervals thereafter until discharge, and finally at about term, it is unlikely that cases were missed. All cases were diagnosed at between 30 and 40 weeks' postconceptual age; this has been found by previous workers.[2 27]

A great many risk factors have previously been associated with the development of retinopathy of prematurity. They include oxygen toxicity,[14] vitamin E deficiency,[11] complications during pregnancy,[10 13] exchange and top up transfusions,[5 8 16] intraventricular haemorrhage,[17] light exposure,[7] gestational age, apnoea, septicaemia,[3] birth weight, indomethacin treatment,[15 18 20] hypercarbia,[5] hypocarbia,[5] and prolonged parenteral nutrition.[5] Many of these data were collected retrospectively, however, leading to uncontrollable bias in the study populations. By prospectively recording the risk factor data in a double blind fashion, so that the examiner was not aware of the history of risk factor exposure in the infant being examined on each occasion, observer bias in the present study has been minimised

Over 50% of the risk factors analysed were found to be significantly associated with the development of retinopathy of prematurity when subjected to unpaired t or χ^2 testing (table 1). Only three factors—acidosis, hyperoxia, and gestational age—were independently associated with the development of retinopathy of prematurity, however, when subjected to stepwise logistic regression analysis.

Similarly the development of more severe retinopathy of prematurity (stages III and IV) was independently associated with acidosis, hyperoxia, and pneumothorax. Risk factor exposure after the first appearance of the disease did not seem to further influence the progression of the disease to more advanced stages. Thus progression to advanced disease seems to be determined by the severity of the early insult to the immature retina and less influenced by prolonged or subsequent insults

While we can conclude from this study that levels of PaO_2 of greater than 12 kPa and pH less than 7·2 are associated with a significantly increased risk of developing retinopathy of prematurity, it is not possible from these data to extrapolate in order to identify values of PO_2 and pH which are 'safe' in these infants. It was also not possible to determine whether a metabolic acidosis alone was significantly associated with the development of retinopathy of prematurity, as acidosis in most infants was either respiratory or of the mixed respiratory and metabolic variety.

The mechanisms by which acidosis and hyperoxia might affect the immature retina leading to retinopathy of prematurity remain speculative. Acidosis is a powerful vasodilator stimulus, and its role in cerebral blood flow regulation is well described.[28] It has also been shown to be associated with the development of intraventricular haemorrhage[29 30] but its role in the regulation of retinal blood flow is not established. Acidosis, however, remains the variable most significantly associated with the disease.[9]

In the eight month period since the completion of this study careful attention has been applied to the early correction of acidosis (pH <7·25) in these very low birthweight infants with the result that not a single case of advanced disease has been seen in this unit.

In order to quantify the reduction in exposure to acidosis and hyperoxia since the completion of this trial and to determine the importance of their reduction in the prevention of progression to advanced disease the collection of risk factor exposure to these variables is still in progress.

We thank Mr V Aber for statistical analysis, Dr L de Vries who performed all the cranial ultrasounds, Mrs A Dennis for typing the manuscript, and Dr M Silverman for invaluable advice and support

The work was supported by a grant from the Hammersmith and Acton Special Trustees and Hammersmith and Queen Charlotte's Special Health Authority

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Accepted 17 August 1987

Archives of Disease in Childhood, 1988, **63**, 528–532

Plasma fibronectin concentrations in breast fed and formula fed neonates

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SUMMARY Plasma fibronectin concentration was measured in neonates of 2 to 5 days of age. Although breast fed and formula fed infants were similar in demographic characteristics, the mean (SD) plasma concentration of fibronectin in 26 breast fed infants, 237 (117) mg/l, was significantly higher than in 27 formula fed infants (171 (91) mg/l). Fibronectin was detected in five colostrum specimens (mean concentration 13·4 mg/l). Similar bands were detected after gel electrophoresis of purified adult plasma fibronectin and whole plasma from breast fed and formula fed neonates after staining or immunoblotting. Fibronectin isolated from breast milk also appeared similar to purified plasma fibronectin. It is possible, although unlikely, that fibronectin is absorbed intact from ingested colostrum. Alternatively, a factor(s) might be present in colostrum that contributes to the regulation of plasma fibronectin concentration.

Fibronectin is a high molecular weight glycoprotein found in plasma and on cell surfaces. Plasma fibronectin acts as a non-specific opsonin, augmenting macrophage and neutrophil phagocytosis, and modulating reticuloendothelial clearance of bacteria and intravascular debris. Therefore it has a potentially important role in host defence against infection. The major sources of plasma fibronectin include hepatocytes, macrophages, and endothelial cells.[1] The concentration of plasma fibronectin is lower in newborn infants compared with children and adults and further decreased in neonates with sepsis.[2]

Human milk has been shown to contain fibronectin that is immunologically cross reactive with plasma fibronectin.[3] We have compared plasma fibronectin concentrations in healthy, term, breast fed and formula fed neonates. In addition, fibronectin concentrations were measured in colostrum and several commercial infants formulas.

Methods

STUDY POPULATION

The study group consisted of healthy term infants who were receiving no medication. Blood for assay was collected two to five days after birth at the time of sampling for state metabolic screening. The following clinical data were recorded. sex, race, method of delivery, indication for caesarean section, birth weight, Apgar scores, and age and weight at time of blood sampling

Colostrum specimens were obtained from five women, two to six days postpartum. Plasma was obtained from healthy, young adults receiving no medications.

Parental consent for blood sampling was obtained according to guidelines established by the Human Subjects Review Committee of Long Island Jewish Medical Center.

SPECIMEN COLLECTION

Blood for assay was collected after heelstick puncture into citrate coated capillary tubes (filled with 19% sodium citrate and baked in an oven until dry). Blood from adults was obtained by venepuncture and injected into citrated tubes (Vacutainer, Becton-Dickinson). Plasma was separated by centrifugation and kept frozen at −20°C until assayed.

Colostrum and mature breast milk specimens were collected into polystyrene tubes after manual expression. Specimens were centrifuged in an Eppendorf microcentrifuge. The fat layer and pellet were discarded and the supernatant was frozen at −20°C until assayed.

Pasteurised whole cows' milk and four commercial infant formulas (Similac, PM 60/40, Isomil (Ross Laboratories), and Prosobee (Mead-Johnson)) were similarly processed.

FIBRONECTIN ASSAY

Fibronectin concentrations were determined by a modification of the competitive enzyme immunoassay previously reported.[4] Microtitre plate wells (Dynatech Laboratories) were coated with purified human plasma fibronectin (Cappel Laboratories) (1 mg/l in 0·01 M TRIS buffer containing 0·15 M NaCl, 0·02% sodium azide, pH 7·4) by overnight incubation at 4°C. The plates were washed five times with phosphate buffered saline 0·05% Tween 20 and blocked with phosphate buffered saline containing 1% bovine serum albumin. A 1:20 000 dilution of rabbit antihuman fibronectin (Cappel) was incubated with increasing concentrations of fibronectin standard or varying dilutions of plasma, colostrum, or commercial milk preparations overnight at 4°C in polystyrene tubes. Antigen antibody mixtures were then transferred to the fibronectin coated, blocked, washed microtitre plate wells and incubated for one hour at 37°C. Plates were then washed and goat antirabbit IgG conjugated to alkaline phosphatase (Cappel) was added to each well and incubated for one hour at 37°C After washing, paranitrophenyl phosphate (Sigma Chemical Company) was added (buffer 0·05 M $NaHCO_3$, 1 mM $MgCl_2$ pH 9·8). The plates were observed for colour development and the optical density of the wells was read on a Dynatech MR 600 plate reader at 410 nm. The concentration of fibronectin in each sample was determined by comparing the optical density of test wells with wells containing known concentrations of fibronectin. All samples were run in triplicate and the mean values determined. The coefficient of variation for individual samples was less than 2%. The results of a given assay were discarded if the correlation coefficient of the fibronectin standards and adjusted optical density values on the plate was less than 0·95.

ISOLATION OF PLASMA AND BREAST MILK FIBRONECTIN

Fibronectin was isolated from adult plasma using gelatin-Sepharose chromatography as previously described.[4] Mature breast milk samples from a single donor were centrifuged at 10 000×g for 30 minutes, the cream was removed, and the sample was respun at 90 000×g for 30 minutes.[3] Fibronectin was isolated from the supernatant sample by gelatin Sepharose chromatography as for plasma fibronectin

ELECTROPHORESIS AND WESTERN BLOTTING

Sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE) was performed in vertical gels with an acrylamide concentration of 6% using a Laemmli buffer system.[5] Samples were reduced with dithiothreitol. Molecular weight standards were purchased from Bio-Rad (Richmond). Gels were stained with Coomassie brilliant blue Identification of fibronectin species in plasma and milk was accomplished by SDS-PAGE followed by electrophorectic transfer of protein to nitrocellulose sheets Immunoblotting was completed by sequen-

Table *Characteristics of patients in study population*

	Breast fed neonates (n=26)	*Formula fed neonates (n=27)*
Sex (male/female)	12/14	12/15
Race (white/non-white)	23/3	23/4
Method of delivery (% vaginal delivery)	58*	78*
Mean (SD) birth weight (g)	3446 (513)	3441 (450)
Mean (SD) Apgar score at 5 minutes	9·7 (0·46)	9·8 (0·46)
Mean (SD) age at time of sampling (hours)	77 (29)†	63 (23)†
Mean (SD) weight on day of sampling (g)	3301 (468)	3373 (440)
Mean (SD) % birth weight lost	4·0 (2·5)‡	1·9 (1·5)‡

*p>0·1, χ^2, 4 fold table, †p>0·05, ‡p<0·001

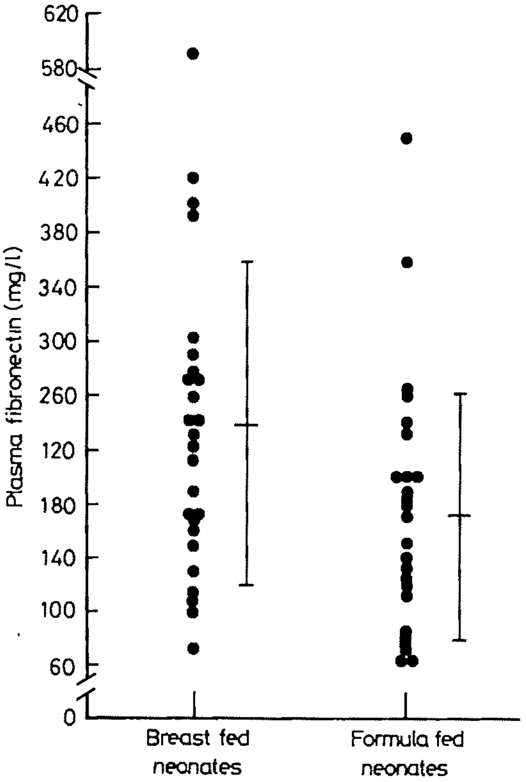

Fig 1 *Fibronectin concentrations in breast fed and formula fed neonates Bars indicate mean and one standard deviation*

tial incubation of nitrocellulose sheets with bovine serum albumin, rabbit antihuman fibronectin (Cappel), perioxidase conjugated goat antirabbit IgG (Bio-Rad), and perioxidase substrate as previously described.[6]

Data were analysed using the Wilcoxon's rank sum test or χ^2 test.

Results

Of the 26 breast fed and 27 formula fed neonates, there were no significant differences between the two groups in sex, race, method of delivery, indication for caesarean section, birth weight, Apgar scores, or age at time of sampling. The percentage of weight lost from birth to time of sampling was significantly greater in the breast fed group (table); however, the magnitude was only 4·0% in the breast fed group compared with 1·9% in the formula fed group.

Plasma fibronectin concentrations were significantly higher in the breast fed newborns compared with the formula fed newborns ($p<0·003$, Wilcoxon's rank sum test). The mean (SD) plasma fibronectin concentration was 237 (117) mg/l in breast fed newborns and 171 (91) mg/l in formula fed newborns (fig 1). The mean (SD) plasma fibronectin concentration in 23 healthy adult volunteers was 576·0 (252) mg/l within the range of previously reported values.[7]

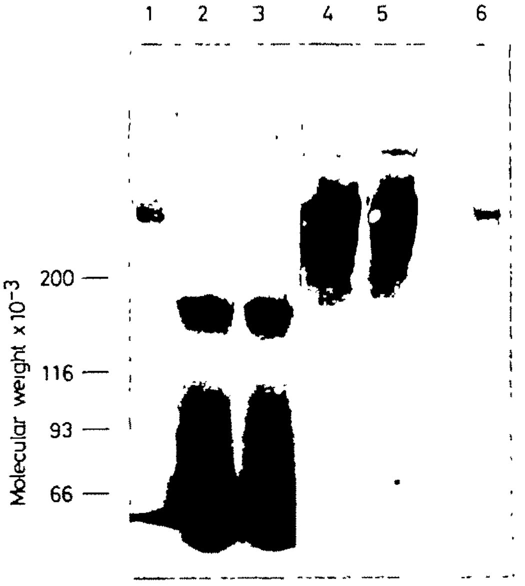

Fig 2 *Sodium dodecylsulphate polyacrylamide gel electrophoresis of plasma from breast fed or formula fed neonates and of fibronectin isolated from breast milk. Lanes 1, 2, and 3 were stained with Coomassie brilliant blue Lanes 4, 5, and 6 were transferred to nitrocellulose and fibronectin was detected using monospecific antibody Lane 1 contains purified adult plasma fibronectin. Lanes 2 and 4 contain 30 μl of pooled plasma from 12 breast fed neonates Lanes 3 and 5 contain 30 μl of pooled plasma from 12 formula fed newborns Lane 6 contains fibronectin isolated from human breast milk.*

The mean (SD) fibronectin concentration in five colostrum specimens was 13·4 (4·7) mg/l (range 6·9–19·5). Fibronectin was not detected in whole cows' milk or four commercial infant formulas The limit of detection for the assay was 0·05 mg/l

Coomassie blue staining after SDS-PAGE showed a doublet in the lanes containing purified adult plasma fibronectin and pooled plasma samples from breast or formula fed neonates which corresponded to a molecular weight of roughly 220 kilodaltons (fig 2, lanes 1–3). Electrophoretic transfer and immunoblotting with antifibronectin antibody showed similar bands in lanes containing purified fibronectin, or plasma from breast or formula fed infants (fig 2, lanes 4 and 5). Even with deliberate overloading of lanes with plasma, there were no lower molecular weight immunoreactive fibronectin fragments detected in the plasma of breast or formula fed neonates Fibronectin isolated from human breast milk also appeared similar to purified human plasma fibronectin (fig 2, lane 6)

Discussion

Our results support previous studies that have observed lower plasma fibronectin concentrations in neonates in comparison with older infants and adults [7] In this investigation we have shown that breast fed neonates have higher plasma fibronectin concentrations than those who were formula fed. The two groups of infants were comparable in demographic and clinical variables. The greater depletion of intravascular volume in the nursing neonates, as evidenced by a greater percentage of weight loss from birth, could be invoked to explain differences in the concentration of a plasma protein; however, even if the entire difference was due to intravascular water, this apparent 2% difference in weight loss could not explain the 39% increase in the plasma fibronectin concentration observed. Inadequate nutrition results in a lowering of plasma fibronectin concentrations.[8 9] Therefore the lower caloric intake of breast fed neonates in the first days of life compared with those formula fed would be predicted to result in a lower concentration of fibronectin in the plasma of the breast fed neonates, not the raised concentrations observed.

Although there was no significant difference in postnatal age between the two groups, the breast fed infants were somewhat older than the formula fed infants. We considered the possibility that the differences in fibronectin concentrations found may in part be influenced by this small difference in age. A significant correlation was found ($r=0{\cdot}477$, $p<0{\cdot}01$) between postnatal age and plasma fibronectin concentrations for the entire group of infants Thus it is possible that the slightly older postnatal age of the nursing infants influenced our findings.[10] When the two groups were analysed independently, however, the correlation reached significance in the breast fed infants ($r=0{\cdot}53$, $p<0{\cdot}01$) but not the formula fed infants ($r=0{\cdot}27$, $p>0{\cdot}10$) If fibronectin concentrations were influenced solely by age, we would expect to observe a positive correlation between postnatal age and plasma fibronectin concentration in the formula fed group.

Because fibronectin may have an important role in opsonisation and clearance of bacteria, decreased concentrations may be a factor contributing to the neonate's increased susceptibility to and mortality from bacterial infection. Though the difference in plasma concentrations observed in breast fed and formula fed neonates is significant, it is unclear whether the 39% higher mean concentration in the breast fed infants is important clinically. As the plasma fibronectin concentrations of adults are more than twice that of neonates, it is clear that there are other factors that have a major role in the regulation of plasma fibronectin concentration. It is not known whether this difference in fibronectin concentration is carried beyond the first few days of life.

We hypothesise several possible mechanisms to account for the differences observed. We have confirmed a previous report that documented the presence of fibronectin in colostrum[3]; therefore, direct absorption of fibronectin may be possible. The significant correlation between postnatal age and fibronectin concentrations in the breast fed infants lends support to this hypothesis As infants who were older would have ingested a larger amount of colostrum, the older breast fed infant might be expected to have higher fibronectin concentrations than his younger counterpart if direct absorption occurred. The similar electrophoretic mobility and immunoreactivity of fibronectin isolated from breast milk and adult plasma precludes the detection of breast milk fibronectin in the plasma of breast fed infants using this method. It is not clear, however, whether a large, protease susceptible protein such as fibronectin could be absorbed intact. Studies have shown that the capacity to absorb macromolecules may be more extensive in the immature small intestine than in the highly developed mature intestine [11] In addition, it has been suggested that in the newborn period, a greater quantity of protein ingested by intestinal epithelial cells escapes intracellular proteolysis as a result of immature lysozymal function, and therefore more protein becomes available for subsequent transport out of the cell and into the circulation.[11] As we assayed immunoreactive fibronectin it is possible that we have measured both intact fibronectin and degraded fragments in plasma. The immunoblot analysis of plasma fibronectin from breast fed infants, however, showed no evidence of fibronectin fragments Furthermore, the difference in plasma fibronectin concentration in breast fed and formula fed infants is not easily accounted for on the basis of fibronectin in breast milk. A newborn ingests more than 500 ml of colostrum in the first three days of life.[12] Given a fibronectin concentration in colostrum of 13 mg/l, the infant would ingest 6·5 mg of fibronectin. Assuming a plasma volume of 150 ml, even complete absorption of ingested fibronectin from the gastrointestinal tract, without intravascular clearance, could account for only two thirds of the increase in plasma fibronectin concentrations observed in the breast fed infants.

A second hypothesis to explain the difference found is that there may be a factor(s) in breast milk that promotes an increase in fibronectin synthesis. This increased production may be specific for fibronectin or may be part of a generalised increase in protein synthesis by hepatocytes, endothelial cells, or other fibronectin producing cells

Alternatively, there may be factors unrelated to absorption of fibronectin from the gastrointestinal tract or to fibronectin production. For example, the plasma half life of fibronectin may be prolonged in breast fed infants

Human milk has been shown to contain several immunologically active elements. Cellular components include macrophages, lymphocytes, and neutrophils; humoral elements include immunoglobulins, lysozyme, and lactoferrin [13] Several studies have shown that breast fed infants have lower infection rates than formula fed infants.[14] A significant association has been found between breast feeding and decreased rates of gastrointestinal illness There is less conclusive evidence that breast feeding may protect against respiratory illness and otitis media.[13] In addition, there appears to be a protective influence of breast feeding on the risk of developing invasive *Haemophilus influenzae* type b disease [15] It is possible that the raised plasma fibronectin concentrations in nursing infants may represent a means by which breast feeding may contribute to their lower risk of infection. Further studies are needed to determine the mechanism that causes the raised plasma fibronectin concentrations in breast fed infants, compared with those who are formula fed, and to determine if this raised concentration persists in later infancy, there is also a need to assess the potential contribution of this quantitative difference in protection of the newborn against infection.

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Accepted 13 November 1987

Archives of Disease in Childhood, 1988, **63,** 533–535

Factors influencing colonisation with gentamicin resistant Gram negative organisms in the neonatal unit

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SUMMARY The proportion of babies colonised with gentamicin resistant Gram negative organisms in a nursery over a 30 month period did not correlate with the quantity or duration of aminoglycosides used, but it did correlate with two indicators of workload: the number of baby days and a score based on the level of nursing care required. Spread of resistant organisms may be more likely as workload increases.

Aminoglycosides are widely used in the treatment of suspected neonatal sepsis so that colonisation and infection with aminoglycoside resistant Gram negative organisms is of major importance. Babies treated with antibiotics for more than three days are more likely to become colonised with Gram negative organisms,[1] and aminoglycoside resistant organisms are more likely to be selected by longer courses of aminoglycosides.[2] Factors other than antibiotic use could be envisaged as being important in determining colonisation with aminoglycoside resistant organisms. It is known that colonisation by organisms with varying sensitivity patterns may fluctuate with time for no clear reason.[3 4] The number of babies in our nursery colonised with gentamicin resistant Gram negative organisms, particularly a gentamicin resistant *Klebsiella oxytoca,* has recently increased. When two babies developed life threatening systemic infections with gentamicin resistant *Klebsiella oxytoca,* we changed from gentamicin to netilmicin as the aminoglycoside used for treating suspected sepsis. We have analysed factors which might be responsible for the emergence of gentamicin resistant Gram negative organisms using surveillance data that were prospectively collected.

Patients and methods

From 1 May 1984 data relating to infection were prospectively collected on all babies admitted to the neonatal unit. The only routine surveillance cultures performed were bacterial cultures of endotracheal secretions taken three times a week from babies receiving artificial ventilation. Bacterial cultures from nose, throat, umbilicus, and rectum and cultures of blood, urine, and cerebrospinal fluid were obtained from all babies with suspected sepsis before starting antibiotics. Specimens were inoculated onto blood agar plates aerobically and anaerobically, MacConkey plates, chocolate agar plates in 5% CO_2, and into cooked meat broth. Organisms were identified according to standard laboratory techniques.[5] Antibiotic susceptibility was determined by the method of Stokes and Ridgway.[6]

The results of bacterial cultures, including the reported antibiotic sensitivities, and the quantity and duration of antibiotics prescribed were prospectively recorded. The number of new aminoglycoside resistant and aminoglycoside sensitive Gram negative organisms cultured in each four week period was recorded. If a baby was colonised with more than one Gram negative organism, each organism was counted. Recolonisation was included if regular cultures showed a baby not to have been colonised for at least two weeks. Identification of organisms was by antibiotic resistance patterns.

The number of babies in the unit each day and the total number of baby days over each four week period was recorded. In addition babies were classified each day as receiving either intensive care, special care, or normal care according to the British Paediatric Association nomenclature.[7] Briefly, *intensive care* signifies continuous skilled supervision by nursing and medical staff, *special care* signifies observation and treatment falling short of intensive care but exceeding normal routine care, while *normal care* is that usually given by the mother in hospital under supervision but requiring minimal medical or nursing involvement.

We have analysed variables that might correlate with colonisation by aminoglycoside resistant organisms. Netilmicin resistance was rare; only four babies in 30 months were colonised with such organisms, so the analysis was performed for gentamicin resistant Gram negative organisms, including organisms resistant to both gentamicin and netilmicin. The proportion of babies colonised with gentamicin resistant Gram negative organisms to babies colonised with any Gram negative organism was compared with the number of baby days of aminoglycosides given, the number of baby days of all antibiotics the weight of aminoglycosides used, the weight of all antibiotics used, and the number of baby days in each four week period from 1 May 1984 until 31 October 1986. The last was used as an index of workload as medical and nursing levels remained virtually constant throughout the 30 month period. In order to get a more realistic measure of workload, based on the estimated relative amount of nursing time required, a workload score was calculated related to the level of care required. Each baby day of intensive care was scored as 5 points, a baby day of special care was scored as 3 points and a baby day of normal care as 1 point.[8] The total score in each four week period was then compared with the proportion of gentamicin resistant organisms Statistical analysis was by Pearson correlation coefficient.

Results

In May 1984, at the start of surveillance, suspected sepsis was treated with benzylpenicillin (in the first 48 hours) or flucloxacillin (after 48 hours) together with netilmicin. In April 1985 (week 56) we changed from netilmicin to gentamicin. The incidence of colonisation with gentamicin resistant Gram negative organisms, mainly coliforms and Pseudomonas, fluctuated over the next two years (see figure) but there were no cases of systemic sepsis due to these organisms In November 1986 (week 117), however, not only was there an increase in colonisation with gentamicin resistant Gram negative organisms but two babies developed systemic sepsis.

We suspected that the incidence of gentamicin resistant organisms might correlate with the quantity of antibiotics used The mean duration of antibiotic courses was analysed for six month periods over the 2½ years. The mean (SD) duration in days of antibiotic courses in each consecutive six month period from 1 May 1984 was 5·45 (4·04), 5·59 (3·66), 4·74 (4·36), 3·61 (4·62), and 4·15 (3·47). It is evident that the increasing incidence of gentamicin resistance was not due to an overall increase in the

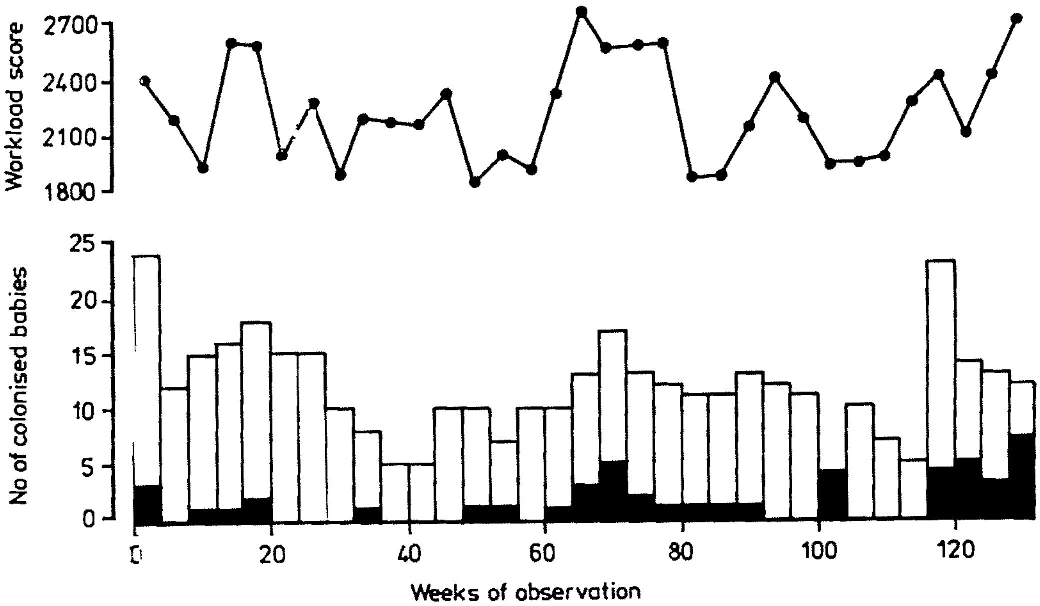

Figure *Relation between workload score in each four week period and number of babies colonised with gentamicin resistant (shaded blocks) and gentamicin sensitive (unshaded blocks) Gram negative organisms* duration of antibiotic courses Furthermore no significant correlation was found between the proportion of gentamicin resistant organisms and the number of baby days of aminoglycosides ($r=0\cdot25$, $p>0\cdot1$), the number of baby days of all antibiotics ($r=0\cdot24$, $p>0\cdot1$), the weight in grams of aminoglycoside used ($r=0\cdot01$, $p>0\cdot1$), nor the weight of all antibiotics used ($r=0\cdot01$, $p=0\cdot1$).

A correlation was found between the number of baby days in each four week period and the proportion of gentamicin resistant organisms ($r=0\cdot42$, $p<0\cdot02$). Furthermore the correlation was even stronger between the score based on the level of intensity of neonatal care and the proportion of resistant organisms ($r=0\cdot50$, $p<0\cdot005$) as shown in the figure.

Discussion

Long courses of aminoglycosides may select for aminoglycoside resistant organisms in an individual baby.[2] The incidence of aminoglycoside resistant organisms in the neonatal unit may depend on other factors such as spread between babies. The importance of handwashing in preventing nosocomial spread of organisms has repeatedly been emphasised.[9] It may be as a corollary of this that understaffing and overcrowding of neonatal units have been shown to correlate with the incidence of infections.[10 11]

We deliberately did not collect colonisation data on all babies as this would have engendered considerable expense. This, however, inevitably made the surveillance incomplete When more babies were being treated it would be expected that more cultures would be sent. For this reason, although there was also a significant correlation between the absolute number of babies colonised with resistant organisms and workload, this might have been an artefact produced by culturing more babies when the unit was busier. Therefore the best measure of incidence of gentamicin resistant Gram negative colonisation was the proportion of babies cultured who were colonised with gentamicin resistant organisms.

We thought initially that the incidence of colonisation with aminoglycoside resistant organisms would correlate with antibiotic use. Because no such correlation was found we examined other variables relating to workload We found significant correlations between measures of workload and colonisation with resistant Gram negative organisms. Resistant organisms may be selected in an individual baby by a long course of antibiotics or introduced by a colonised baby transferred from another hospital We were able to identify one baby in each of these categories as apparently initiating an 'outbreak' of colonisation with a particular resistant organism, although no formal identification was performed other than antibiotic resistance patterns. On other occasions the source of the resistant organism was not found. Spread of resistant organisms between babies may be more likely when the workload is high and normal aseptic precautions become compromised.

Aminoglycoside resistant organisms may colonise babies without causing systemic sepsis.[3 4] We do not change our antibiotic policy on the basis of colonisation data alone, although as colonisation precedes late onset systemic sepsis, widespread colonisation with resistant organisms is worrying. We consider the occurrence of cases of systemic sepsis due to organisms that are not covered by our antibiotic policy to be an indication to change the aminoglycoside in use.

David Isaacs is funded by the Wellcome Trust We thank the staff of the special care nursery, the medical and technical staff in the Public Health Laboratory Service, Christopher Pierce of the Nuffield Department of Medicine for statistical advice, and Maggie Ellis for typing the manuscript

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Accepted 4 January 1988

Archives of Disease in Childhood, 1988, **63,** 536–540

Quantitative bacterial flora of acute appendicitis

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SUMMARY A quantitative bacteriological study of the appendix wall of 43 children admitted to this unit showed no significant differences between the flora of the histologically normal and acutely inflamed appendices. Bacteroides species, *Escherichia coli,* and streptococcal species were the commonest organisms isolated and were found in counts of 10^3 to 10^8 organisms per gram of tissue. Bacteroides species were most commonly the dominant flora in both normal and inflamed appendices.

The lack of increased counts of organisms in acute inflammation of the appendix suggests an unfavourable environment to bacterial proliferation making primary bacterial infection an unlikely aetiological factor in the pathogenesis of appendicitis.

Acute appendicitis is the commonest surgical emergency in childhood, although its aetiology in most cases is unproved. Most workers have found the qualitative flora of appendicitis does not differ appreciably from that of the normal appendix in adults and children.[2 3] Both *Streptococcus milleri* and *Bacteroides fragilis,* however, have been implicated in the pathogenesis of appendicitis by increased isolation rates in acute inflammation.[4 5] Less is known of the quantitative flora of the acutely inflamed and normal appendix. In adults anaerobic bacteria are more commonly found in counts of above 10^6 colony forming units/ml than aerobic bacteria in acute inflammation,[6] and anaerobic bacteria, in particular bacteroides species, have been quantified in acutely inflamed and normal appendices.[7 5]

There are no data of the quantitative flora as a whole from appendix tissue in the normal and inflamed states. This quantitative study was undertaken to show the numerically dominant flora and compare more precisely the flora of the acutely inflamed and histologically normal appendices.

Method

Forty four children admitted to the paediatric surgical unit at Southampton General Hospital and undergoing appendicectomy between 10 November 1978 and 2 April 1979, were studied. One child who had received antibiotics within two weeks of admission was excluded from the study.

The excised appendix was divided logitudinally and inspissated material removed One half was sent for histological examination, the other subdivided transversely into tip and proximal sections. The individual sections were weighed, placed in transport medium (Todd Hewitt broth, 0·1% cystine hydrochloric acid and 10% glycerol by volume) and homogenised under nitrogen. The homogenate was stored over liquid nitrogen. Serial log dilutions of the homogenate were later made and plated on a selection of media (Mac-Conkey, chocolated, vpt (an agar containing vancomycin, polymixin, and trimethoprim), blood neomycin, and anaerobic agar) and incubated under the appropriate aerobic, microaerophilic, and anaerobic conditions.

Counting was performed with a Gallenkamp colony counter. Dominant isolates were purified by subculturing and identified Bacteroides species were identified using the Analytical Profile Index 20A system[8] and streptococcal isolates by Lancefield grouping, fermentation of sugars, and growth on special media.[9 10]

Log mean counts for each organism were compared between the inflamed and normal groups by the t test and within individual appendices by the paired t test. Isolation rates between the two groups were compared by the χ^2 test

Results

Of the 43 children included in the study (age range 5 years 2 months to 15 years 3 months), 29 histologically confirmed cases of appendicitis were found of which four had clinically perforated. Thirteen histo-

Table 1 *Isolation rates and combined counts of anaerobic bacteria in normal and acutely inflamed appendices*

Organism	*Histologically normal (n=14)*			*Acutely inflamed (n=29)*		
	No (%)	*Counts/g*	*Mean*	*No (%)*	*Counts/g*	*Mean*
Bacteroides fragilis	3 (21)	$3\ 1^{7}-1\ 4^{8}$	$6\ 0^{7*}$	11 (38)	$1\ 0^{3}-3\ 2^{8}$	$3\ 2^{7*}$
Bacteroides thetaiotaomicron	8 (57)	$2\ 4^{4}-4\ 2^{8}$	$1\ 3^{7}$	10 (35)	$1\ 1^{3}-2{\cdot}2^{8}$	$6\ 4^{7}$
Bacteroides distasonis	1 (7)	$1{\cdot}3^{7}$	—	4 (14)	$5{\cdot}8^{5}-2\ 7^{8}$	$4\ 0^{7}$
Bacteroides ovatus	1 (7)	$8\ 5^{7}$	—	1 (3)	$4\ 2^{5}$	—
Bacteroides vulgatus	1 (7)	$1\ 8^{8}$	—	0	—	—
Clostridium welchii	8 (57)	$5\ 8^{1}-1{\cdot}9^{4}$	$8\ 6^{2}$	10 (35)	$6{\cdot}0^{1}-1\ 4^{3}$	$4\ 8^{2}$
Anaerobic streptococci	0	—	—	2 (7)	$9\ 1^{5}-2{\cdot}4^{7}$	$1\ 2^{7}$

$*n^{x}=n\times10^{x}$

Table 2 *Isolation rates and combined counts of streptococcal species in normal and acutely inflamed appendices*

Organism	*Histologically normal (n=14)*			*Acutely inflamed (n=29)*		
	No (%)	*Counts/g*	*Mean*	*No (%)*	*Counts/g*	*Mean*
Streptococcus milleri	5 (36)	$4{\cdot}4^{5}-1{\cdot}8^{7}$	$1\ 3^{7*}$	13 (45)	$1\ 4^{4}-1\ 6^{8}$	$4\ 5^{7*}$
Streptococcus salivarius	4 (29)	$7{\cdot}6^{3}-1\ 4^{7}$	$3\ 8^{6}$	4 (14)	$1\ 9^{5}-4\ 2^{7}$	$1\ 5^{7}$
Streptococcus mutans	2 (14)	$1\ 2^{5}-3\ 5^{6}$	$1\ 8^{6}$	4 (14)	$1\ 8^{3}-7\ 5^{5}$	$5\ 7^{4}$
Streptococcus sanguis	2 (21)	$1\ 7^{7}-1{\cdot}8^{8}$	$6\ 2^{7}$	2 (7)	$5\ 5^{4}-2\ 8^{6}$	$1\ 1^{6}$
Streptococcus anginosus	1 (7)	$4\ 8^{5}$	—	2 (7)	$3\ 1^{3}-1{\cdot}5^{4}$	$9\ 0^{3}$
Streptococcus mitior	1 (7)	$3\ 2^{6}$	—	3 (10)	$3\ 2^{3}-9{\cdot}8^{6}$	$3\ 2^{6}$
Streptococcus bovis	0	—	—	1 (3)	$7{\cdot}0^{7}$	—
Streptococcus agalactiae	1 (7)	$7{\cdot}4^{4}$	—	1 (3)	$1\ 3^{5}$	—
Streptococcus zooepidemicus	1 (7)	$6{\cdot}6^{7}$	—	0	—	—

$*n^{x}=n\times10^{x}$

Table 3 *Isolation rates and combined counts of aerobic bacteria in normal and acutely inflamed appendices*

Organism	*Histologically normal (n=14)*			*Acutely inflamed (n=29)*		
	No (%)	*Counts/g*	*Mean*	*No (%)*	*Counts/g*	*Mean*
Escherichia coli	14 (100)	$1{\cdot}4^{4}-1\ 8^{8}$	$4\ 4^{6*}$	24 (83)	$2\ 1^{3}-9{\cdot}7^{7}$	$1\ 4^{7*}$
Pseudomonas species	4 (29)	$6{\cdot}9^{4}-7\ 2^{6}$	$1\ 4^{6}$	2 (7)	$5\ 6^{4}-7{\cdot}6^{4}$	$6\ 7^{4}$
Streptococcus pneumoniae	0	—	—	2 (7)	$4\ 9^{3}-2{\cdot}0^{7}$	$8{\cdot}7^{6}$
Staphylococcus aureus	2 (14)	$6{\cdot}1^{3}-8\ 1^{6}$	$2\ 3^{5}$	1 (3)	$1{\cdot}3^{3}$	—
Haemophilus parainfluenzae	0	—	—	1 (3)	$1\ 2^{7}$	—
Non-lactose fermenting coliform	0	—	—	1 (3)	$4\ 3^{5}$	—
Campylobacter	1 (7)	†	—	0	—	—

$*n^{x}=n\times10^{x}$

†Counts impossible owing to colony swarming

logically normal appendices were found at operation and in one case the appendix was removed incidentally.

ISOLATION RATES

The differing isolation rates of *B fragilis*, *B thetaiotaomicron*, and *S milleri* in the two groups were not significant at the 5% level (table 1) Neither were there any significant differences in the isolation rates of other streptococcal species, aerobic, or anaerobic bacteria between the two groups (tables 2 and 3) Bacteroides species, *E coli*, and streptococcal species were not isolated in between 10%–17% of acutely inflamed or perforated appendices There was, however, only one inflamed appendix in which none of these organisms was present (the flora comprised a mixed growth of *Haemophilus parainfluenzae* and *H pneumococcus*).

BACTERIAL COUNTS

The counts of the isolated organisms showed no significant differences within individual appendices ($p>0{\cdot}05$). Between normal and inflamed appendices there was no significant difference in the counts of

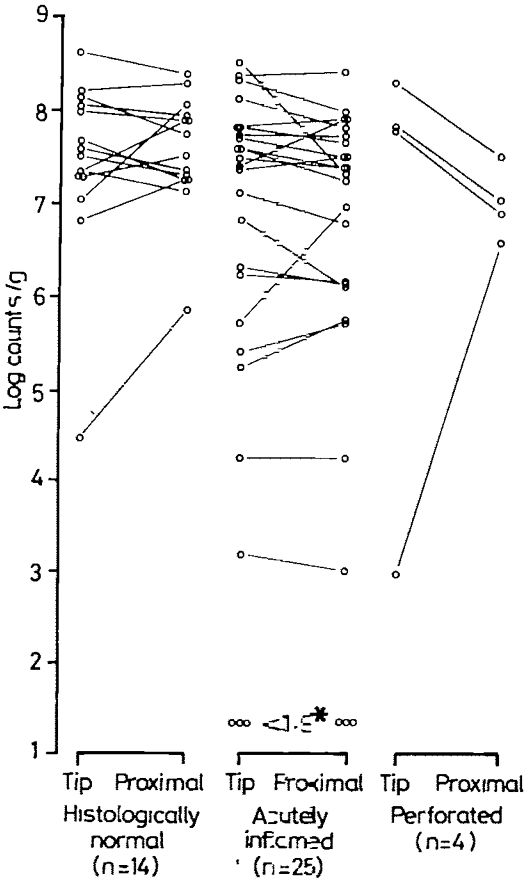

Fig 1 *Log colony counts of tip and proximal sections for all bacteroides species in each group of appendices.*
** Minimum sensitivity of method when organism not isolated*

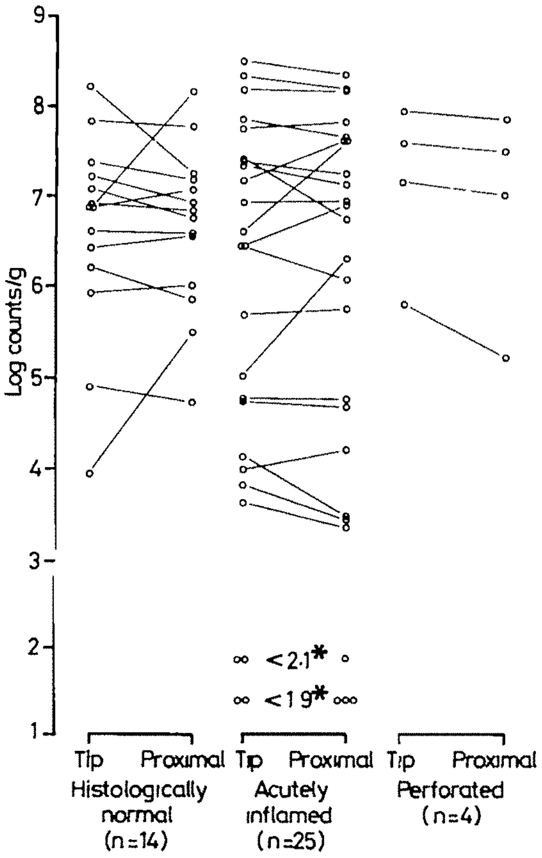

Fig 2 *Log colony counts of tip and proximal sections for all streptococcal species in each group of appendices*
** Minimum sensitivity of method when organism not isolated*

all streptococcal isolates ($0\cdot05<p<0\cdot1$), but the difference was significant for *E coli* and the combined bacteroides species ($0\cdot02<p<0\cdot05$) This difference was not apparent if the appendices in which the organism was not isolated were excluded from the comparison (figures 1, 2, and 3). Tables 1, 2, and 3 also indicate the range of counts found for individual organisms in each group of appendices.

DOMINANT BACTERIA

Table 4 shows that bacteroides species were the predominant organisms in most normal and acutely inflamed appendices.

Discussion

This study confirms no qualitative difference in the flora of the acutely inflamed and normal appendices, *E coli* and bacteroides species being the commonest aerobe and anaerobe respectively, in both groups. Isolation rates are very variable depending on the site cultured and methodology[11] Ghnassia *et al,* for example, isolated bacteroides species from only 2% of luminal swabs.[3] The method of grinding of the appendix wall, combined with methods to preserve anaerobes during processing, enables high isolation rates of all organisms.

The age range in this study differs from most qualitative and all quantitative studies, which have tended to use adults, or adolescents and adults. Although it is highly likely that the bacterial flora is similar in all these age groups, this has not been verified. In addition to variation in technique, this makes valid comparisons between this and other studies more difficult.

No significant difference in the isolation rates of *S*

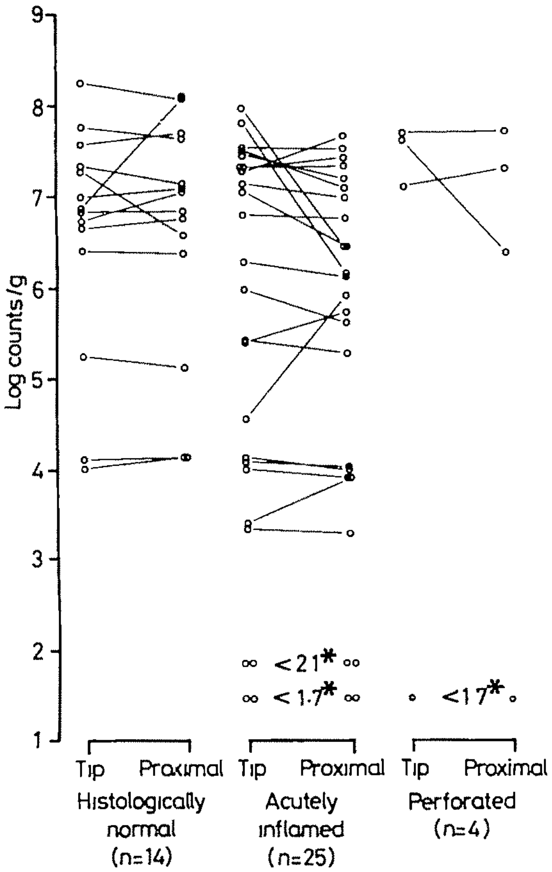

Fig 3 *Log colony counts of tip and proximal sections for Escherichia coli in each group of appendices*
**Minimum sensitivity of method when organism not isolated*

milleri between normal and inflamed appendices was found, contrary to Poole and Wilson who found this organism in 30% of 13 normal and in 60% of 79 acutely inflamed appendices in the under 20 years age group.[4] The appendix, however, has been confirmed to be an important reservoir for *S milleri,* which is a common pathogen in postappendicectomy sepsis in children.[12]

The most comparable studies of the anaerobic bacterial flora of the appendix have been carried out in two studies by Werner *et al.*[5 7] They made a quantitative study of the luminal contents of 49 acutely inflamed appendices and 11 incidental appendicectomies and found bacteroides species in 87·8% of acutely inflamed appendices, with counts of between 10^3–10^9/g and in all incidental appendices with counts of 10^4–10^{10}/g.[5 7] The acutely inflamed appendices were from all ages and the incidentals from women undergoing gynaecological laparotomy. The counts obtained by Werner *et al* were similar to those found in this study

In the same studies *B fragilis* was detected in 80% and *B thetaiotaomicron* in 55% of acutely inflamed appendices, compared with normal large bowel flora where *B thetaiotaomicron* predominates and *B vulgatus* is found in 43% of cases. This study shows an apparently increased isolation rate of *B fragilis* in acute inflammation (from 21% to 38%) but this was not found to be significant. More recently Elhag *et al* found an identical isolation rate of 41% for *B fragilis* in normal and acutely inflamed appendices[2] Although this would appear to exclude *B fragilis* as a primary pathogen in appendicitis, it undoubtedly has an important role as a secondarily invasive organism causing appendicial sepsis.[2 6]

The consistently lower isolation rates for bacteroides species in this study, compared with those of Werner *et al* is most likely due to only the dominating Gram negative anaerobe in each case being identified.

The counts of bacteroides, *E coli,* and streptococci when present in the appendix, do not significantly differ between the normal and acutely inflamed state, although the tissue ischaemia in acute appendicitis would be expected to favour overgrowth of anaerobic and microaerophilic organisms.[13] The lack of increased counts in acute inflammation suggests that the environment for bacterial proliferation is unfavourable. In addition, as grinding of the appendix would be expected to

Table 4 *Numerically dominant organisms of the appendix flora in histologically normal and inflamed appendices*

Organism	*Histologically normal (n=14)*		*Acutely inflamed (n=29)*	
	No	*% Dominant*	*No*	*% Dominant*
All bacteroides	14	93	26	76
Bacteroides fragilis	3	21	11	35
Bacteroides thetaiotaomicron	7	50	10	28
Bacteroides distasonis	1	0	4	10
Escherichia coli	14	7	24	10
All streptococcal species	14	0	25	10

liberate all organisms to the homogenate, the lack of increased counts suggests that the number of organisms invading the wall is low in comparison with those in the lumen or mucosally associated. This would favour the spread of bacteria through the appendix wall during inflammation as being a passive process secondary to the loss of viability of the wall as has been shown to occur with obstruction of the lumen.[14,15]

I would like to thank Professor P Watt and Mr D Drake for their invaluable advice and guidance in this work, and Mr NF Freeman for his encouragement and advice in preparing this paper

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Accepted 2 December 1987

Archives of Disease in Childhood, 1988, **63**, 541–559

Short reports

Air embolism in ventilated very low birthweight infants

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SUMMARY Five cases of air embolism in ventilated very low birthweight infants are reported. In all cases the outcome was fatal with the babies dying at about 15 hours of age.

Pulmonary air leaks are well recognised complications of ventilatory support in the newborn period[1] Most of these leaks are confined to the tissue spaces within the thoracic cavity but in 1970 Gregory and Tooley reported a case of air embolism diagnosed on an *x* ray film taken at necropsy.[2] We report five cases of this uncommon complication seen in this hospital in the last six years and draw attention to the clinical features of this uniformly fatal condition.

Case reports

Case 1. A girl weighing 960 g was born after spontaneous onset of labour at 26 weeks' gestation Only minimal resuscitation was required (Apgar scores 8 and 10) but she rapidly developed increasingly severe respiratory distress necessitating ventilation, and severe generalised pulmonary interstitial emphysema was noticed on chest radiography. Her condition deteriorated and she died at 19 hours of age. Just before death a sample from the umbilical artery catheter was seen to contain bubbles of air and bubbles of gas were seen to appear from a heel prick performed to sustain the diagnosis of air embolism; this was confirmed by an *x* ray film taken before necropsy.

Case 2. A boy weighing 1175 g was born by elective caesarean section at 28 weeks' gestation because of an antepartum haemorrhage. An earlier premature onset of labour at 24 weeks' gesatation had been halted with intravenous salbutamol. He required ventilation from birth but quickly developed pulmonary interstitial emphysema and it proved impossible to maintain his oxygenation. Just before his death, at 14 hours of age, sampling of the umbilical artery catheter showed air in the vessel and air embolus was confirmed on an *x* ray film taken immediately after death.

Case 3. A boy weighing 1170 g was delivered by emergency caesarean section at 28 weeks' gestation after a prolonged liquor leak after the mother's membranes had ruptured at 24 weeks He was intubated from birth and it was difficult to maintain adequate ventilation. At 14 hours of age the baby suddenly deteriorated; the legs and abdomen became white and air was seen in the blood sample drawn from the umbilical artery catheter. The transcutaneous oxygen electrode was reading 18 kPa at the time. A chest *x* ray film taken before death showed a right pneumothorax, pneumomediastinum, and air in the ventricular cavity and outlining the major vessels.

Case 4. A boy weighing 880 g, the second of twins, was born by a breech delivery at 28 weeks' gestation after spontaneous rupture of the membranes 48 hours before He was intubated from birth and his condition remained stable until at 15 hours of age he became visibly white with no cardiac output The cardiac monitor registered a supraventricular tachycardia. The air entry on the right side was reduced and the insertion of a chest drain resulted in spontaneous resolution of the supraventricular tachycardia to sinus rhythm. A pneumothorax occurred on the left side almost simultaneously. There was still no cardiac output and because the indwelling umbilical artery catheter oxygen electrode was reading >20 kPa blood was withdrawn from the umbilical artery catheter and this contained air bubbles. A chest *x* ray film taken just before death showed bilateral pneumothoraces, pneumomediastinum, and air in the ventricles and outlining the major vessels (figure).

Case 5. A boy weighing 630 g was delivered at 24 weeks' gestation by an emergency caesarean section four days after an amniocentesis for polyhydram-

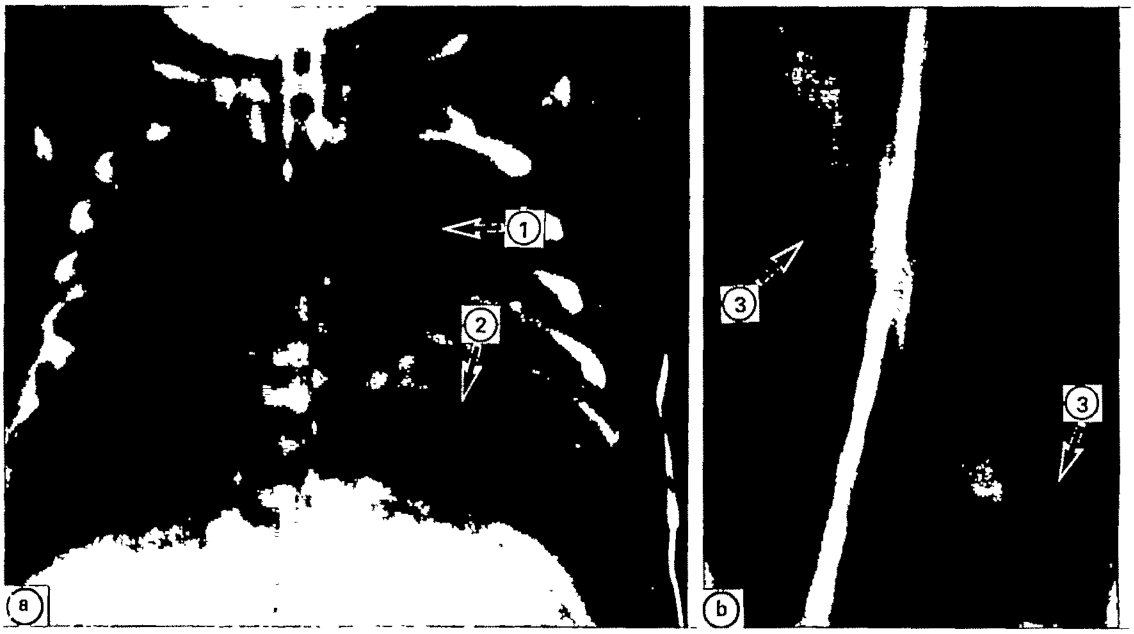

Figure *Chest x ray film taken just before death in case 4 (a) This shows the bilateral pneumothoraces and a penumomediastinum (1), air in the ventricle can be seen (2) (b) The area surrounding the left humerus has been enlarged to show air in the brachial vein (3). (The structure lying across the arm is the lead from the transcutaneous oxygen electrode)*

nios The mother had been treated with antibiotics before delivery because of a fever and the infant received antibiotics from birth The baby required ventilation from birth because of severe respiratory distress that appeared on chest *x* radiography to be due to surfactant deficiency. By 18 hours of age his respiratory condition had worsened despite the use of tolazoline and volume support and he required very high pressures to maintain his oxygenation At 19 hours of age he suddenly deteriorated becoming mottled and blue despite the indwelling oxygen electrode reading 18 kPa. 'Squelchy' heart sounds were heard on auscultation and a chest *x* ray film showed air in the chambers of the heart and great vessels and support was withdrawn.

The clinical details of the five infants are shown in the table.

Discussion

All five of these babies suffered massive air embolism with no evidence of accidental injection of air

Table *Summary of clinical details of the five infants*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Gestation (weeks)	26	28	28	26	24
Weight (g) [Centile]	960 [50%]	1175 [60%]	1170 [50%]	880 [50%]	630 [50%]
Prolonged rupture of membranes	–	–	+	+	–
Antepartum haemorrhage	–	+	–	–	–
Start of intermittent positive pressure ventilation	4 hours	Birth	Birth	Birth	Birth
Maximum positive inspiratory pressure (cm H_2O)	25	30	37	28	47
Maximum mean airways pressure (cm H_2O)	18	17	21	18	44
Lowest mean blood pressure (mm Hg)	21	26	28	31	17
Time of death (hours)	19	14	15	15	19
Last continuous PO_2 reading (kPa)	18	3 8	2 5	20	18
Other Air Leaks					
Pneumothorax	–	–	–	+	–
Pneumomediastinum	–	–	+	+	–
Pneumopericardium	–	–	–	–	–
Pulmonary interstitial emphysema	+	+	–	+	–

via syringes or infusion sets. Death occurred rapidly after the event but in three patients antemortem chest *x* radiography confirmed the diagnosis and lead to immediate cessation of attempts at resuscitation. Clinical features which alerted us to the diagnosis in the three last patients were the pallor of the infant,[2] the discrepancy between the state of the baby and the high readings of the continuous oxygen monitor, and finally the presence of air in the samples drawn from the umbilical artery catheter. The presence of supraventricular tachycardia in the fourth case is interesting and to our knowledge air embolism has not previously been recorded as a precipitating cause for this arrythmia.

In the early reports of this complication the babies tended to be of longer gestation (range 25–34 weeks) and emphasis had been placed on the higher pressures (range 28–90 cm H_2O) that had been used.[2 3] It is noteworthy that the pressures in the first four infants in this study (like those in a similar infant reported by Rudd and Wrigglesworth[4]) were lower (25–37 cm H_2O) although they were obviously much higher than we would like to use. Three of the babies had pulmonary interstitial emphysema in which it is thought high peak airways pressure used during ventilation for hyaline membrane disease plays a causative role.[5] Four out of the five infants had proved difficult to oxygenate and the use of this high pressure was determined by the evidence of atelectasis on the chest *x* ray film.

Four of the five infants had an additional form of air leak to their air embolism and it seems likely that the air enters the circulation after rupturing out of the pulmonary air spaces. Whether this occurs at the site of weakness in the pericardial reflection near the ostia of the pulmonary veins is not clear.[6] Two of the subjects had prolonged rupture of the membranes (in one case four weeks) but there was no evidence that either pulmonary hypoplasia or infection played a role in the pathogenesis of their embolism, although congenital infection may have played a role in the fifth subject. There was no evidence of meconium aspiration or inappropriate resuscitation at birth that might have predisposed these infants to this disaster nor was there any evidence of accidental introduction of air through the peripheral or central cavities. All infants were appropriate for gestational age and there was no evidence of any underlying congenital disorder.

It is of interest that in the patients reported here death occurred at about 15 hours of age. In our experience this parallels the time course of the peak severity in the respiratory distress experienced by these very low birthweight immature babies. In our unit 42% of ventilated babies, <26 weeks' gestation, develop air leaks. It seems likely that air embolism represents the extreme end of the range of air leaks that occur in very immature lungs.

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Accepted 1 December 1987

Clostridium difficile and acute enterocolitis

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SUMMARY *Clostridium difficile* belonging to groups not normally detected in infancy was the only potential pathogen detected in the stools of two infants with severe enterocolitis. Further information regarding the virulence of this organism was obtained by use of a recently introduced typing scheme.

Clostridium difficile is not usually considered to be of clinical importance in stool specimens from infants because this organism can also be found as part of their normal gut flora.[1] In adults, *C difficile* is rarely isolated from normal faecal specimens and its overgrowth with production of toxin, secondary to antibiotic treatment, can result in the development of pseudomembranous colitis. In infancy there are only occasional reports of this condition.[2 3] The introduction of typing schemes for *C difficile* has provided evidence for the existence of different types of this organism with variable virulence [4-6]

The two infants described below presented with severe enterocolitis and *C difficile* was the only potential pathogen found It was possible to place the *C difficile* isolates into two unusual groups, not commonly found in young infants This was established by the use of the typing scheme primarily used for epidemiological purposes, based on the incorporation of sulphur-35-labelled methionine into the cell proteins and their separation by gel electrophoresis.[4]

Case reports

Case 1. A 2 month old girl was referred from another hospital with a two day history of refusing feeds and 24 hour history of profuse non-bloody diarrhoea with one episode of vomiting. She was lethargic and tachypnoeic with a temperature of 40°C. No medicines had been given before the symptoms began but she had been started on benzylpenicillin and gentamicin at the referring hospital after the development of a noticeably distended abdomen.

Biochemical investigations gave normal results for urea and electrolytes. Her haemoglobin concentration was 95 g/l, white cell count $4\cdot4\times10^9$/l, and platelets normal. A barium study showed no evidence of malrotation. There was no growth from blood culture, and cerebrospinal fluid showed no cells and no growth. Culture of her stools gave negative results for campylobacter, enteropathogenic *Escherichia coli*, salmonella, and shigella species. Five representative *E coli* cultures from the stool were sent to Dr B Rowe at the Enteric Reference Laboratory, Colindale and these were identified as *E coli* 013 (a non-enteropathogenic serotype) which did not produce heat stable or labile toxin, or verotoxin. No viruses were seen on electron microscopy or grown from faecal samples. Serology for *Yersinia enterocolitica* and *pseudotuberculosis* did not show raised titres. *C difficile* was grown from the infant's stools and was shown to be highly toxigenic for both the cytotoxin and the enterotoxin and further typing showed that it belonged to group X. Cytotoxin was also detected directly from the stool specimen.

Over the next 24 hours the child's haemoglobin dropped to 78 g/l and an emergency laparotomy was carried out. Intravenous metronidazole was added to the antibiotic treatment preoperatively. Large quantities of clear yellow peritoneal fluid were found but no organisms were seen on Gram stain and no growth was obtained from culture. Dilated loops of ileum were noted and the distal half of the ileum was oedematous with the terminal 2 cm appearing to be bruised. No evidence of appendicitis or intussusception was found. The patient's condition improved dramatically after the operation. She was maintained on antibiotics and her diarrhoea diminished gradually over the next few days.

Case 2. A 3 week old girl was admitted with a 24 hour history of profuse watery, offensive, but non-bloody diarrhoea. She had no history of vomiting Four days before admission she had been given an anticholinergic drug, pipenzolate bromide, which was initially prescribed at twice the normal dose for her age and weight This was given at double the prescribed dose by her parents and the diarrhoea had started 24 hours after stopping this drug.

Biochemical investigations gave normal results for urea and electrolytes. Her haemoglobin was 143 g/l, white cell count $20\cdot5\times10^9$/l, neutrophils 28%, platelets $25\,000\times10^9$/l. There was no growth from blood culture, and cerebrospinal fluid showed no cells and no growth. Numerous stool cultures gave negative results for enteropathogenic *E coli*, salmonella, shigella, and campylobacter species. No antibodies were detected against yersinia species and no stool viruses were seen on electron microscopy or grown from tissue culture. *C difficile* was cultured from stool specimens and its cytotoxin was also identified directly from one stool The organism was a potent producer of enterotoxin and cytotoxin and further typing showed that it belonged to group W

Thirty six hours after admission the child developed abdominal distension Moderate gaseous distension of large and small bowel was noted with occasional fluid levels apparent. She was given intravenous benzylpenicillin, gentamicin and metronidazole, and oral feeding was completely stopped. Her abdominal wall became distended and oedematous; she passed blood in her stools and 'coffee ground' fluid was aspirated through her nasogastric tube. Her white cell count rose to $38\,000\times10^9$/l (47% neutrophils) and bowel sounds could not be heard. She was given nine days total parenteral nutrition; her general condition slowly improved and the diarrhoea gradually stopped.

Discussion

Both these infants were seriously ill and none of the pathogens normally associated with diarrhoea in infancy were found. Neither of the children had been given antibiotics before onset of symptoms but one of them had been given an inappropriate dose of an anticholinergic drug. The advisibility of giving infants drugs that may interfere with gut motility and indirectly influence the composition of the gut flora should be questioned.

The renal function in both infants remained normal and excluded haemolytic uraemic syndrome. *E coli* isolates from one of the infant's stools were further investigated for production of toxins, including verotoxin, but these were not detected Neither child had a colonoscopy performed and biopsy specimens for histological examination were therefore not available.

One of the infants had group X *C difficile* identified and the organism was a potent producer of both enterotoxin and cytotoxin This group has caused an outbreak of antibiotic associated colitis in patients on oncology wards.[4] The other infant had a highly toxigenic group W *C difficile* identified—the usual groups found in newborn infants are A–D.[4] Group W has been isolated from an adult with pseudomembranous colitis (unpublished data) and this organism was also found to be a high producer of toxins A and B.[6]

It seems probable that *C difficile* had clinical importance in these two infants. Both children appeared to respond to treatment with intravenous antibiotics, including metronidazole, which is effective against the organism. Possible pathogenic significance of *C difficile* in the gut of infants with severe enterocolitis should not be discounted on the basis that this organism may also be found in stools of normal children in this age group The use of typing schemes, often used for epidemiological purposes, may help elucidate the potential pathogenic role of *C difficile* in individual patients and also determine whether specific antimicrobial treatment should be urgently instituted.

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Accepted 10 February 1988

AIDS encephalopathy with response to treatment

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SUMMARY A 3 year old boy who had acquired HIV infection transplacentally developed the classical features of AIDS encephalopathy, spastic diplegia and expressive aphasia. His computed tomogram showed cerebral atrophy. Treatment with zidovudine and weekly infusions of gammaglobulin led to considerable clinical improvement and an almost normal computed tomogram nine weeks later

A boy was identified as HIV antibody positive at the age of 21 months after his mother presented and died of pneumonia due to *Pneumocystis carinii* She was HIV antibody positive and had received two units of blood after the birth of her first child. The source of her infection remains unclear. The first child is well at age 6 and has no detectable HIV antibody. Our patient, the second child, is thought to have acquired HIV transplacentally.

The boy was born after a full term normal delivery, birth weight 3150 g, and he received all conventional immunisations, including measles, without problem. His head circumference, weight, and length had grown along the 50th, 10th, and 10th centiles, respectively. His development was normal, and he had been walking normally since age 13 months and, aged 21 months, was starting to join words. The only clinical abnormality was moderate inguinal lymphadenopathy.

Initial investigation showed normal T lymphocyte subsets (fig 1) and a normal number of T helper cells. He had a grossly raised IgG (37 g/l) concentration but no IgG virus antibodies (including measles and polio) were detected; this suggested impaired production of functional antibody. IgM isohaemagglutinins were present. Delayed type hypersensitivity skin tests with passive phytohaemagglutinin gave normal results.

At the age of 22 months he developed pertussis that was proved on culture. Despite early treatment from day seven of the illness with erythromycin, *Bordetella pertussis* could still be isolated at 28 days. Age 25 months he developed unilateral submandibular lymphadenitis with *Streptococcus pyogenes* cultured from the fauces. This responded rapidly to drainage (culture negative) and intravenous benzylpenicillin. His T4 cells were now depleted (fig 1) and IgG concentrations were diminished. One month later he developed a right lower lobe pneumonia with a heavy growth of *Haemophilus influenzae* from pharyngeal secretions. Despite physiotherapy and appropriate antibiotics there was little clinical response but high dose intravenous cotrimoxazole gave rapid resolution.

Over two weeks during this illness his speech rapidly regressed to expressive aphasia with only vowel sounds but with no cognitive impairment He also rapidly developed a considerable spastic diplegia with inability to walk A computed tomogram showed cerebral atrophy (fig 2) Sensory and motor nerve conduction studies gave normal results. His cerebrospinal fluid showed no white cells and normal concentrations of glucose and protein. No bacteria, fungi, or viruses were cultured. IgG antibodies to HIV were selectively increased in the cerebrospinal fluid. The antibody to albumin ratio given by the equation

$$\frac{[\text{HIV in cerebrospinal fluid}-\text{IgG}]}{[\text{Serum HIV}-\text{IgG}]}\times\frac{[\text{Serum albumin}]}{[\text{Albumin in cerebrospinal fluid}]}$$

was 110 (upper limit of normal is 2), indicating production of HIV antibody in the cerebrospinal fluid, and is evidence of HIV infection within the nervous system.

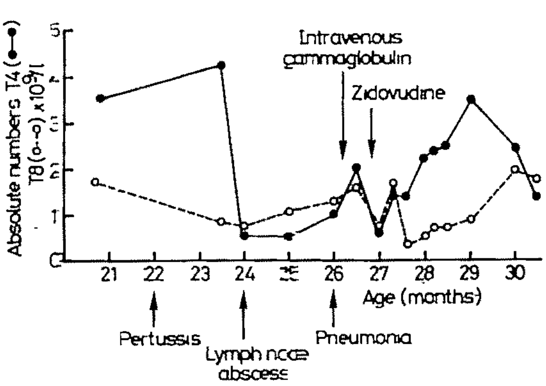

Fig 1 *Changes in T lymphocyte subsets*

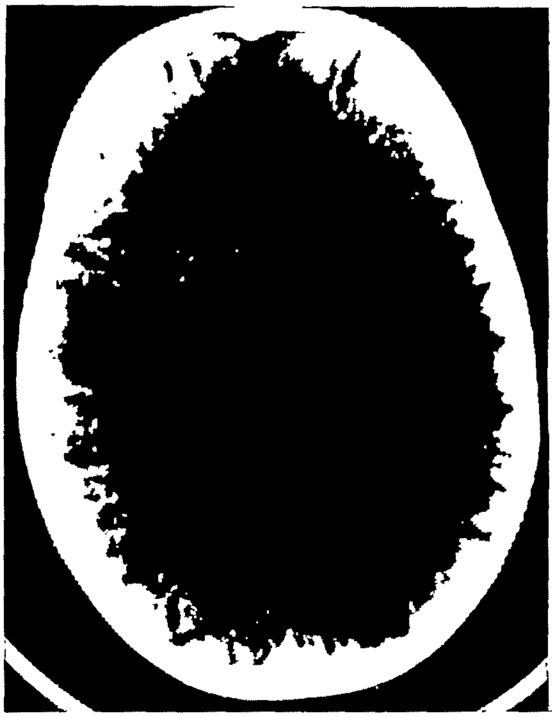

Fig 2 *Initial computed tomogram.*

The patient was treated with intravenous gammaglobulin 300 mg/kg. He was initially treated weekly because his IgG concentration was 14·2 g/l; he was also given oral zidovudine (Retrovir) 100 mg/m^2 four times a day, equivalent to 16 mg/kg/day. This thymidine analogue selectively inhibits DNA chain elongation of the HIV but does not eradicate the viral genome from infected cells. Treatment with zidovudine and intravenous gammaglobulin every four weeks has continued for eight months. The intravenous preparation of zidovudine was given orally without acceptance problems and we have seen no haematological or neurological toxicity. A plasma profile of zidovudine showed a peak of 2·9 μM of active drug with 10·9 μM of glucuronide metabolite one hour after ingestion.

The boy has been cared for at home by his father and his general well being has remained good over eight months. He is now gaining weight normally. Spasticity has regressed allowing him to run unaided across the room, and his reflexes are now normal. He can articulate several single words. A repeat computed tomogram after nine weeks treatment showed considerable improvement (fig 3). His

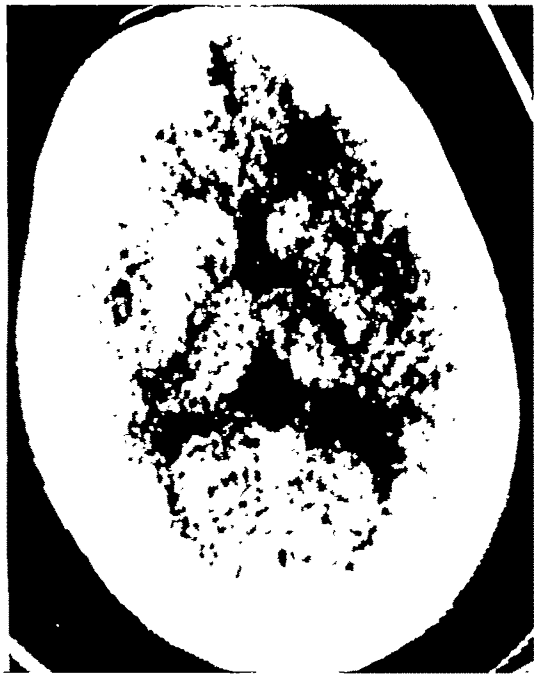

Fig 3 *Computed tomogram after nine weeks treatment This cut is at the same level as fig 2*

lymphocyte subsets initially became more normal but T4 concentrations fell 12 weeks after starting zidovudine (fig 1). These have now returned to normal (not shown in figure).

Discussion

AIDS encephalopathy in childhood usually presents with language deficits, developmental regression, pyramidal signs, and cortical atrophy. The encephalopathy may be static or progressive and, untreated, is associated with a very bad prognosis.[1] Data have only recently become available that suggest that children with HIV encephalopathy may improve when treated with zidovudine with or without intravenous gammaglobulin (S Blanche and PA Pizzo. Abstracts presented at the Wellcome International Antiviral Symposium, Monte Carlo, 2–4 December 1987). There are reports of neurological improvement in adults treated with zidovudine [2]

The response to zidovudine may be dose dependent. Using 100 mg/m^2 intravenously for two weeks followed by 100 mg/m^2 orally four times a day, a French group reported eight children with HIV encephalopathy of whom two became normal, three had a partial improvement, and three no real improvement (S Blanche Abstract presented at the Wellcome International Antiviral Symposium, as above). These early results compare with the American experience of administering doses two to three times as great by continuous intravenous infusion This was associated with noticeable improvement in all encephalopathic children, but unfortunately also with a high incidence of catheter related infections (PA Pizzo. Abstracts presented at the Wellcome International Antiviral Symposium, as above).

The immunological improvement could, however, be attributed in part to intravenous gammaglobulin.[3] The fall in T4 numbers 12 weeks after starting zidovudine is consistent with recent reports.[4] At this dose of zidovudine we saw no toxic effects with haematological indices, liver and kidney function remaining normal. Marrow suppression during zidovudine treatment, however, is as common in children as in adults.[3]

Zidovudine is an expensive drug in limited supply. As the dose depends on weight, more children than adults can be treated for the same cost. We believe this case should encourage others to use zidovudine in children with AIDS encephalopathy. Further studies will be required to determine the optimum dose, whether combination treatment of zidovudine plus acyclovir or gammaglobulin confers benefit, for how long treatment should continue, and whether neurological improvement is maintained.

We are grateful to Dr Yap and the Scottish National Blood Transfusion Service for the supply of gammaglobulin and to the Wellcome Foundation Ltd for supplies of Retrovir solution

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Accepted 30 December 1987

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Nephrogenic diabetes insipidus, cystinosis, and vitamin D

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SUMMARY We describe a patient with early diagnosed cystinosis who presented with nephrogenic diabetes insipidus in addition to proximal tubular dysfunction. Another feature in this patient was abnormally low serum concentration of 24,25 dihydroxy vitamin D_3 ($24,25(OH)_2D_3$) with normal 25 hydroxy vitamin D_3 ($25(OH)D_3$) and relatively low 1,25 dihydroxy vitamin D_3 ($1,25(OH)_2D_3$).

Cystinosis is a disorder of cystine metabolism with autosomal recessive inheritance In this disease cystine is stored intracellularly in the lysosomes. There are three known clinical forms of cystinosis: nephropathic-infantile, intermediate-juvenile, and the adult onset type, which is the only form where the kidneys are unaffected.[1]

The nephropathic form has been described with a variety of clinical manifestations Almost all patients present with polydipsia, polyuria, anorexia, failure to thrive, growth retardation, typical brown yellowish skin and hair, rickets, hepatosplenomegaly, and corneal and retinal involvement. The laboratory findings reflect the biochemical abnormalities of Fanconi syndrome, hypothyroidism, and somatomedin C deficiency.[2 3]

In this report we describe unusual tubular dysfunctions and an interesting abnormality in vitamin D metabolism in an early diagnosed case of cystinosis.

Case report

A girl aged 25 months was admitted because of polydipsia, polyuria, and failure to thrive; the symptoms had begun at 8 months of age. Pregnancy and delivery were uneventful. Birth weight was 4500 g Family history showed that three of the child s siblings had died two boys and one girl. One boy had suffered from polydipsia and polyuria and died at the age of 2½ years. Another boy had died after intractable vomiting and diarrhoea at 6 months of age, and one girl died from an unknown cause at the age of 4 months. The other members of the family and two parents were healthy. Developmental milestones were normal in our patient.

On admission the child's weight was 7900 g and the height was 71 cm, both below the third percentile. Heart rate was 116 beats/minute and blood pressure was 100/70 mm Hg. Physical examination was otherwise normal.

Laboratory investigations showed hyponatraemia with serum sodium concentration of 129 mmol/l (normal range 135–145 mmol/l) and hypokalaemia with serum potassium concentration of 2·9 mmol/l (normal range 3·5–5·0 mmol/l), serum urea concentration of 9·3 mmol/l (normal range 1·5–7 mmol/l), and creatinine concentration of 119 µmol/l (normal 80 µmol/l) Serum alkaline phosphatase activity was 822 IU/l (a normal result for this age is less than 300 IU/l), serum phosphorus concentration ranged between 0·96 and 1·43 mmol/l (normal range for this age 1·4–2·0 mmol/l), and calcium concentration was 2·4 mmol/l (normal range 2·0–2·6 mmol/l). Glucose, total protein, albumin, and liver enzymes were within normal limits. Capillary pH was 7·4 (normal range 7·38–7·42), serum bicarbonate was 20 mmol/l (normal range 20–23 mmol/l). Urinalysis showed traces of albumin and glucose on several occasions. Tubular reabsorption of phosphorus was 67% (normal 85%). A random urine osmolarity measurement was 114 mmol/kg H_2O. Urinary output was 2000 ml/24 hours.

An *x* ray film showed that her bone age was in the lower range for her chronological age. There was no radiological evidence of rickets.

A seven hour water deprivation test terminated by an intranasal deamino-8-D-arginine vasopressin (DDAVP) test was performed.[4] Urine osmolarity increased from 121 mmol/kg H_2O to 148 mmol/kg H_2O only Therefore the diagnosis of nephrogenic diabetes insipidus was made. Treatment by hydrochlorothiazide and indomethacin caused a reduction in urinary output to 1000–1400 ml/24 hours, cessation of polydipsia, improvement in appetite, and a weight gain of 500 g within one week.

At the age of 32 months she had grown only 3 cm during the previous seven months. Hepatosplenomegaly and clinical signs of rickets were first detected. Her growth retardation became more pronounced than the lag in weight gain and was appreciably below the third percentile (74 cm) A brown yellowish colour of her skin and hair was noticed.

Laboratory investigations showed metabolic acidosis (pH 7·28, serum bicarbonate concentration 15 mmol/l), persistence of high serum urea and creatinine concentrations, low serum phosphorus, high alkaline phosphatase activity and normal calcium concentration. Serum sodium and potassium concentrations were normal.

Vitamin D metabolites concentrations were: $1,25(OH)_2D_3$ 59 76 pmol/l, $25(OH)D_3$ 67·6 nmol/l, both in the normal range (>46·8 pmol/l, >39 nmol/l, respectively). Concentrations of $24,25(OH)_2D_3$ 1·42 nmol/l, 1·15 nmol/l, and 1·17 nmol/l were found in three separate samples (normal 2·5–10 nmol/l by high performance liquid chromatography depending on 25(OH)vitamin D concentration).[5] Concentrations of thyroid hormones were triiodothyronine (T_3) 3·06 nmol/l (normal range 1·25–3·14 nmol/l) and thyroxine (T_4) 130·8 nmol/l (normal 59–158 nmol/l).

Results of urine examinations were: pH 6·5–7 and the glucose and protein traces intermittently persisted. Tubular reabsorption of phosphorus was 63%, nephrogenous cyclic adenosine 5 monophosphate (cAMP) was 1438 pmol/ml glomerular filtration rate (GFR) (normal 1000–2000 pmol/ml GFR). Chromatography of the urine did not show aminociduria.

Bone *x* ray films showed severe rachitic changes. Bone age corresponded to 1½ years. Intravenous pyelography and kidney ultrasonography gave normal results

Bone marrow aspiration showed cystine crystals. There was a high free cystine content of peripheral leukocytes· 4·14 μmol ½ cystine/g of protein (50 times results from normal controls). Both findings were consistent with cystinosis. Slit lamp microscopy did not visualise corneal cystine crystals. Treatment with 1 mmol/kg/day sodium bicarbonate corrected the metabolic acidosis and her appetite improved. Indomethacin was stopped because of high serum creatinine and urea concentrations but no improvement was noticed. During a follow up of one year, tubular disturbances continued Tubular reabsorption of phosphorus was 64% and glycosuria appeared more often. Urine osmolarity was 162 mmol/kg H_2O after 10 hours of water deprivation. Treatment included bicarbonate, hydrochlorothiazide, and cysteamine.

Discussion

Nephrogenic diabetes insipidus as the initial presentation of cystinosis has been described in only a few cases.[2] It is possible that some patients with cystinosis with polyuria and polydipsia who are not routinely subjected to an antidiuretic hormone (ADH) test escape the diagnosis of nephrogenic diabetes insipidus. This specific test has not been performed in almost all the previously reported cases. We can assume, therefore, that the tubular defect in cystinosis may also affect the distal nephron. It is noteworthy that the proximal tubular abnormalities in this patient did not include aminoaciduria but the phosphaturia and occasional glycosuria were prominent findings. The former led to the clinical bone disease. In previous reports describing early diagnosed cases of cystinosis there were some patients showing an incomplete form of tubular defects referred to as 'partial Fanconi syndrome.'[2]

The possibility of nephropathic cystinosis in this girl was raised because of the presence of 'nephrogenic diabetes insipidus', which as an isolated defect is inherited as a sex linked disease rarely found in such severity in female patients.

Analysis of serum vitamin D metabolites concentrations showed that the $24,25(OH)_2D_3$ concentrations in our patient were much lower than those described in patients with vitamin D resistant rickets from other etiologies. Their fraction of total serum $25(OH)D_3$ was 2% in our patient, in comparison with 10% in normal children (figure) [5] Serum $1,25(OH)_2D_3$ and $25(OH)D_3$ concentrations were normal, but in view of low serum phosphate the concentration of $1,25(OH)_2D_3$ can be considered as relatively low

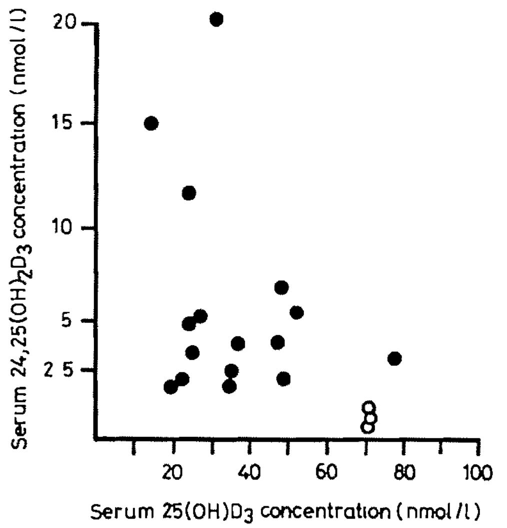

Figure *Relation between serum 24,25 dihydroxy vitamin D_3 ($24,25(OH)_2D_3$) and serum 25 hydroxy vitamin D_3 ($25(OH)D_3$) concentrations in 16 normal children (●)[5] and in our patient (○)*

It is possible that 24-hydroxylase activity in the kidney is much more sensitive to the specific metabolic changes of cystinosis than that of α-1-hydroxylase.

Although the phosphate leak, per se, could account for the pathogenesis of rickets, one cannot rule out that the low concentration of 24,25$(OH)_2D_3$ could also contribute to the bone disease in this patient.[6]

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Accepted 27 October 1987

Ophthalmitis in meningococcal disease

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SUMMARY We report an infant with meningococcal septicaemia and meningitis who had panophthalmitis at presentation that was unresponsive to standard systemic antibiotic treatment but which responded to topical steroid and mydriatic treatment The pathogenesis may have been immune mediated

Case report

The patient, a 7 month old boy in whom there was no important family or perinatal medical history, had been unwell for three days before admission with cough, poor feeding, and diarrhoea. (On questioning later his mother recalled noting that his eyes were 'blood shot' two days before admission.) On the day of admission he deteriorated and developed a widespread rash On admission he was ill but not shocked or hypotensive. Axillary temperature was 39°C and he had a widespread purpuric rash but no conjunctival petechiae, although both bulbar conjunctivae were injected. He was very irritable, noticeably photophobic, and had meningism. A clinical diagnosis of meningococcal meningitis was made and the following initial investigations performed: cerebrospinal fluid was turbid with $4{\cdot}56\times10^9$/l leucocytes, glucose 0·1 mmol/l, total protein 2·6 g/l with raised globulins; Gram staining showed Gram negative diplococci, and both cerebrospinal fluid and blood culture subsequently confirmed *Neisseria meningitidis* (later reported as Group C) sensitive to benzylpenicillin and chloramphenicol. Peripheral blood count showed: haemoglobin 110 g/l, white blood count $22{\cdot}8\times10^9$/l with 57% neutrophils and platelets 312×10^9/l

Treatment was started with intravenous benzylpenicillin 300 mg/kg/day and his general condition gradually improved Photophobia persisted as well as low grade fever, however, although his meningism resolved and there were no localising neurological signs On the seventh day of treatment a repeat examination of the cerebrospinal fluid gave normal results, and a computed tomogram was normal with no evidence of abscess or subdural collection. Antibiotic treatment was stopped on the eighth day

An ophthalmological opinion was obtained 12 days after admission as his eyes continued to be red, and he was photophobic with a low grade temperature The appearances were suggestive of uveitis with limbal injection; and he had miosed non-reactive pupils, fibrinous exudates in the anterior chamber, and a dull red reflex. Topical treatment with prednisolone 0·5% drops and cyclopentolate 1% was started and within two days he had considerably improved, he was not feverish and had minimal photophobia.

An examination under general anaesthetic later confirmed the diagnosis of anterior uveitis, dilated iris vessels and posterior synechia were found in both eyes. The pupils continued to be poorly dilated and phenylephrine 2·5% drops were added to the topical regime The eyes were of normal size and the intraocular tension, measured by applantation tonometry, was in the normal range He continued to improve and was discharged after 24 days.

Further investigations including screens for autoantibodies and serology, including herpes simplex, and tests for cytomegalovirus, toxoplasma, toxocara, Reiter protein reagin, and *Treponema pallidum* haemagglutination antibody gave negative results.

On subsequent ophthalmic review the anterior uveitis continued to settle and as the pupils gradually became more dilated it was possible to see that there was also posterior uveitis in both eyes The media were still clearing after two months and topical steroid treatment was continuing By six months the vitreous had cleared of all posterior uveitis and the topical steroid was stopped.

Discussion

Eye disease in acute meningococcal infection is rare but well reported.[1–4] Two examples of primary acute meningococcal conjunctivitis are described by Shuttleworth and Benstead which responded to appropriate topical antibiotic treatment [1] Cases of eye disease occurring with acute systemic infection (meningococcaemia or meningitis), however, are more common. For example, Koch and Carson in 1958, reported three cases of uveitis in 128 children [2] In a more detailed description, a 7 year old girl with acute meningococcaemia and concurrent severe endophthalmitis was reported—the response to parenteral penicillin and chloramphenicol and topical steroid treatment was rapid and complete.[3]

In a large study of acute meningococcal infection Whittle *et al* found six cases of 'episcleritis' (defined as inflammation of the sclerae) in 717 patients studied in Northern Nigeria; five of them also had arthritis. Both complications were seen six to nine days after the onset of the illness and were mild, and they resolved completely without specific treatment. Slit lamp examination was not available to these authors They postulate that episcleritis, arthritis, and cutaneous vasculitis in their patients are 'allergic' complications due to immune complex disease—immunological studies in four patients with arthritis or cutaneous vasculitis showed the presence of circulating meningococcal antigen at presentation with deposits of antigen, immunoglobulin, and C3 in synovial fluid white cells and skin biopsy specimens in some patients [5] Meningococcus has been isolated by paracentesis of the eye in patients with meningococcal infection, this supports the likelihood of locally produced immune complexes rather than circulating complexes.[6]

In this child, despite successful treatment of Group C meningococcal septicaemia and meningitis, the ophthalmitis and indeed systemic symptoms, as manifested by low grade fever and general malaise, were unresponsive to standard antibiotic treatment, unlike previously reported cases. The response to topical steroid and mydriatic treatment was dramatic, however, although treatment was needed for six months until resolution was complete We believe that the ophthalmitis was initiated by primary meningococcal infection but perpetuated by a continuing immunological response due to local immune complex deposition. The severity and persistence of the ophthalmitis in this case, is, we believe, unique and we have no explanation for its occurrence in this child. Clinicians should actively seek evidence of ophthalmitis in cases of acute meningococcal infection: clinical pointers include persistent photophobia, red eyes, and miosed nonreactive pupils.

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Accepted 30 December 1987

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Phototherapy and the use of heat shields in very low birthweight infants

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SUMMARY The irradiance produced by phototherapy units in use on a neonatal unit was measured. The phototherapy tubes were found to decline at a variable rate Heat shields used to decrease heat and evaporative losses in the very low birthweight infant reduce irradiance and may appreciably limit the effectiveness of phototherapy.

Phototherapy is an accepted treatment for neonatal hyperbilirubinaemia and reduces the need for exchange transfusions.[1] A dose response relationship has been established with a peak response observed to blue light with a spectral range 420–470 nm. A saturation point exists (between 1 and 3 mW/cm^2) beyond which further increases in irradiance do not produce further increases in the rate of fall of serum bilirubin.[2 3] A minimum irradiance of 1 mW/cm^2 in the 420/480 nm range has been recommended to produce an optimum effect.[3]

Irradiance from phototherapy decreases with time due to the natural decay of the fluorescent bulbs. There is a sharp drop during the first 72 hours of use. In 200 hours, 20% or more of the irradiance in the blue wavelength may be lost. Recommendations for bulb replacement vary from 200 to 2000 hours.[4]

Transparent thermal blankets, plastic hoods, and perspex heat shields are widely used to reduce heat and evaporative losses in the very low birthweight infant (<1000 g).[5 6] The extent to which these coverings reduce the irradiance reaching these infants has not been reported

This study was established to assess the output of phototherapy units currently in use on a regional neonatal intensive care unit and to determine the effect on irradiance of measures to reduce evaporative and heat losses.

Methods

Seven Vickers Medical phototherapy units were in use at the time of the study Each was fitted with four 40 watt Vickers Medical blue 600 mm tubes. These had been changed six months before the start of the study. Digital clocks had been fitted to each unit allowing the hours of use to be calculated The number of phototherapy hours of each phototherapy unit since the last change of bulbs was recorded.

Each unit was set up over an incubator (Vickers Medical Model 79). The distance between the phototherapy tubes and the mattress was measured. The irradiance produced by each unit was recorded on three occasions using an irradiance meter (MaCam R450) The optical detector of the irradiance meter was a solid state photodiode with optical filters with a spectral response matching the bilirubin phototherapy action spectrum between 430–475 nm The detector head had been modified with a cosine corrected diffuser giving a 180° field of view The sensor had a peak sensitivity at 450 nm and half maximum sensitivities at 429 and 475 nm. The range of measurements was from 0 to 1·2 mW/cm^2 The top of the optical detector was 4 cm above the base of the irradiance meter at a similar height above the mattress as the body surface of the preterm infant. Calibration was checked by a standard that had been calibrated to the specifications of the United States National Bureau of Standards.

The irradiance meter was placed on the mattress in the incubator and its position adjusted to give an optimum recording. After recording the peak irradiance produced by each phototherapy unit the bulbs were renewed and the irradiance compared.

A thin plastic sheet, a plastic bubble blanket (thermal blanket) designed for industrial packing, and a clear perspex plastic headbox (26 cm×26 cm×15 cm) all used as heat shields, were compared by placing each over the top of the optical detector of the radiometer and measuring the irradiance reaching an infant.

Results

The irradiance produced by each phototherapy unit was found to increase to a peak value 60–90 seconds after starting phototherapy A progressive reduction in irradiance was observed when the output of six phototherapy units was then recorded at 15 minute intervals for two hours. A steady state was reached at a mean time of 45 minutes (range 30–90 minutes) after the start of phototherapy with no further reduction over a 24 hour period. The irradiance produced showed a mean (SD) reduction of 24% (0·5) from the initial peak recording. After allowing the phototherapy bulbs to cool after disconnection of the units, the irradiance increased to the previous peak levels.

The number of phototherapy hours recorded on each unit varied from 1382 to 2499 hours. There was no correlation with peak irradiance produced ($r=-0{\cdot}56$ $p>0{\cdot}05$). The peak irradiance recorded varied from 0·24 to 0·53 mW/cm^2 (table 1). On renewing the phototherapy tubes, the irradiance increased from 0·5 to 3·7 times as shown. The distance from the phototherapy unit bulbs to the mattress was 42 to 43 cm for all units except 1 and 7. The stands of these two units were taller increasing the distance to 51 cm. The irradiance produced by these units reached 0·58 and 0·64 mW/cm^2 only, after the change of tubes. When these units were lowered to 43 cm the irradiance increased by 50% and 60%, respectively

The effect of the heat shields on the irradiance reaching an infant was measured in triplicate, two hours after starting phototherapy The reduction in irradiance recorded with each covering, using each phototherapy unit, was expressed as a percentage of the steady state irradiance. The mean was calculated and the effect of the coverings compared (table 2) The perspex heat shield and single layer plastic sheet had less effect than the thermal blanket in which an 11·4% reduction in irradiance was observed. When a perspex heat shield in addition to a double layer of plastic or bubble sheet was used, a 17% and 25% reduction in irradiance was recorded, respectively.

Table 1 *Phototherapy hours and peak irradiance recorded from seven phototherapy units in current use and peak irradiance achieved with new tubes*

Phototherapy unit No	*Time (hours)*	*Peak irradiance mW/cm²*	*Irradiance of new phototherapy tubes mW/cm²*
1	1382	0·24	0·58
2	1626	0·50	1·00
3	1800	0·48	0·92
4	2217	0·53	0·86
5	2390	0·46	0·98
6	2462	0·28	1·04
7	2499	0·42	0·64

Table 2 *Reduction of steady state irradiance (mean percent (SD)) of six phototherapy units after optical detector of irradiance meter covered by a heat shield*

	Single	*Double*	*Quadruple*
Plastic sheet	7·0 (0·8)	12·5 (0·8)	23·1 (1·2)
Thermal blanket	11·4 (1·3)	19·4 (1·2)	—
Perspex heat shield	5·3 (1·1)	—	—
Plus plastic sheet	11·4 (1·0)	17·0 (0·8)	—
Plus thermal blanket	16·9 (1·8)	25·1 (1·7)	—

Discussion

A considerable variation in the irradiance produced by the phototherapy units was found. The peak irradiance recorded from two of these units, No 1 and 6, was minimal (0·24 and 0·28 mW/cm^2, respectively). There was no correlation with the hours of use; this shows the variable rate of decay of the blue phototherapy tubes. These tubes emit substantially more energy across the 425–475 nm wavelengths than broad spectrum bulbs. However, they are known to decay faster. The irradiance of two of the phototherapy units was decreased because of the increased distance of the bulbs from the mattress and a simple adjustment corrected this. Reducing the distance between phototherapy tubes and infant has been shown to increase the effectiveness of phototherapy [3]

Measures to reduce heat and evaporative losses in the low birthweight infant may reduce the effectiveness of phototherapy. A reduction in the steady state irradiance by 5·3% was recorded with a perspex heat shield, 7% with a single plastic sheet, and 11·4% with a thermal blanket. Where difficulty in maintaining body temperature is encountered there is a tendency to increase the number of plastic layers. This reduces the irradiance further. A reduction of 25·1% of the steady state irradiance was observed if a double thermal blanket plus perspex shield was used. Depending on the output of the phototherapy unit used, such reductions may appreciably alter the effectiveness of the phototherapy

The sick extremely low birthweight infant (<1000 g) is particularly at risk from hyperbilirubinaemia With the complications and hazards of exchange transfusions it is important that the phototherapy treatment available for any neonate is optimal The output of all phototherapy units should periodically be checked and the above factors relating to its use taken into consideration.

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Accepted 30 November 1987

Gall bladder distention in newborns

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SUMMARY Three cases of gall bladder distention in asphyxiated newborns are described Clinical and ultrasound examination showed this to be a benign, transient phenomenon. A causal relation between tissue hypoxia and gall bladder distention is proposed.

Gall bladder distention in neonates has only recently been described by several authors,[1–6] but considerable conjecture regarding the pathophysiology of this finding exists as reflected by the numerous hypotheses proposed. Lack of enteral feeding,[2 3] sepsis,[4] hepatic vein engorgement,[5] and transient functional disturbance of gall bladder motility[6] have all been implicated as causes of gall bladder distention.

Transient gall bladder distention occurring in three asphyxiated neonates is described and an hypothesis linking this phenomenon with tissue hypoxia is proposed.

Case reports

Case 1. An asphyxiated boy, weighing 4100 g, was delivered by caesarean section at 42 weeks' gestation. Apgar scores were 3 and 4 at one and five minutes, respectively. The initial blood pH was 7·16 with a base deficit of 12·2 The immediate neonatal course was complicated by seizures, acute tubular necrosis, ileus, and urinary retention. On the third postnatal day, a large, firm mass was palpated in the right hypochondrium extendings to below the level of the umbilicus. Ultrasound examination showed a distended gall bladder measuring 4·6×2 cm (fig 1). Nasogastric feeds of expressed breast milk were introduced on the fourth postnatal day. The mass remained palpable until the 13th day. A repeat ultrasound examination on day 11 confirmed resolution of the enlargement. An unconjugated hyperbilirubinaemia was prolonged, but not severe. Blood cultures were sterile

Case 2. A boy, weighing 2350 g, was delivered by caesarean section after fetal distress at 36 weeks' gestation. The Apgar scores were not accurately recorded, but the blood pH was 7·09 and base deficit 14·5 There was no conclusive evidence for acute tubular necrosis, ileus, or urinary retention. The infant was severely hypotonic, however, and remained so during the period of hospital care A firm, regular mass was palpated in the right hypochondrium on the third day. Ultrasound examination showed a distended gall bladder measuring 4×1·3 cm (fig 2). The mass was not clinically

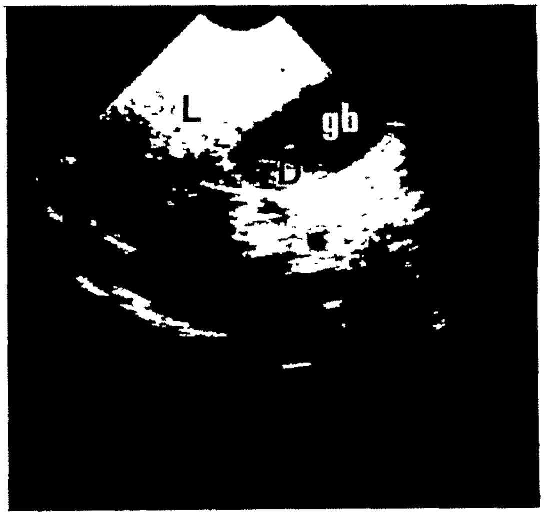

Fig 1 *Ultrasound picture taken on third postnatal day showing distended gall bladder containing debris in case 1 (L=liver, gb=gall bladder, and D=debris).*

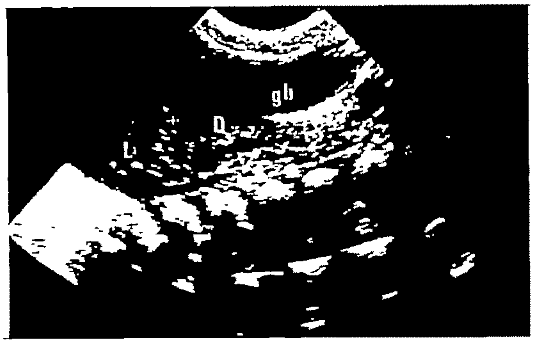

Fig 2 *Ultrasound picture taken on third postnatal day showing distended gall bladder containing a small amount of debris in case 2 (L=liver, gb=gall bladder, and D=debris)*

detectable on the sixth day. Nasogastric feeds of expressed breast milk were introduced on the fifth day. A mild hyperbilirubinaemia was of short duration. Blood cultures were sterile.

Case 3. A boy, weighing 1100 g, was delivered vaginally at 30 weeks' gestation. Apgar scores were 2 and 6 at one and five minutes, respectively Aggressive resuscitation was required. An early blood gas analysis was not performed. The immediate postnatal course was complicated by apnoeic spells and acute tubular necrosis. On the third day, a right sided abdominal mass was palpated An ultrasound examination confirmed the presence of a distended gall bladder, measuring 4·9×1·6 cm. A grade III intraventricular haemorrhage was observed on cranial ultrasound. Blood cultures were sterile. Nasogastric feeds of expressed breast milk were initiated on the fourth day. By the 10th day the abdominal mass was no longer palpable. A moderate unconjugated hyperbilirubinaemia was short lived.

Discussion

Asphyxia neonatorum is known to reduce blood flow to expendable, splanchnic organs, in favour of flow to more vital organs. The hypoxia suffered by these splanchnic organs may result in an ileus, necrotising enterocolitis, acute tubular necrosis, and atonic distention of the urinary bladder We believe this mechanism to be causal in the three cases of gall bladder distention described above.

The hypoxia produced by reduced splanchnic blood flow may cause hollow organ dysfunction in two ways. Firstly, a direct effect upon smooth muscle function or secondly, by autonomic nerve dysfunction.

Most previously described cases have occurred in the settings of an ill newborn with respiratory distress syndrome[3] or septicaemia[4] in which tissue hypoxia was most likely. Two authors[2 5] have described gall bladder distention in the asphyxiated newborn, however, they did not link the findings. We conclude that tissue hypoxia may have an important pathophysiologic role in producing transient gall bladder distention in ill neonates

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Accepted 11 November 1987

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Circumcision and periurethral carriage of *Proteus mirabilis* in boys

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SUMMARY Swabs were taken for culture from the periurethral area and urethral meatus in 124 uncircumcised and 60 circumcised boys. *Proteus mirabilis* was grown from 28 (22·6%) swabs from uncircumcised boys and from only one (1·7%) swab from circumcised boys. This supports the idea that the prepuce may be the source of proteus urinary tract infection

Differences in the pattern of bacteria causing urinary tract infection are age and sex related. *Proteus mirabilis* features more prominently as a urinary pathogen in boys than girls.[1] It is unclear why this difference occurs. Periurethral colonisation may be an important event as a prelude to ascending infection through the urethra [2] Furthermore one study has shown that the difference in bacterial aetiology with age and sex in children with urinary tract infection correlates with a similar variation in the periurethral flora.[3]

There is little information on the periurethral flora, particularly proteus carriage of circumcised boys, perhaps due to the difficulty in obtaining sufficient numbers of subjects. We sampled the periurethral flora in uncircumcised and circumcised normal boys.

Table 1 *Comparison of organisms cultured from uncircumcised and circumcised boys*

Organism	*No (%) of uncircumcised boys (n=124)*	*No (%) of circumcised boys (n=60)*
Proteus mirabilis	28 (22 6)	1 (1 7)
Streptococci	6 (4·8)	7 (11 7)
Escherichia coli	5 (4·0)	0
Staphylococcus aureus	1 (0 8)	1 (1 7)
Bacteroides	1 (0 8)	0
Commensals/no growth	87 (70·2)	51 (85 0)

Patients and methods

The patients sampled in the survey were either inpatients or outpatients of the National Children's Hospital who had conditions unrelated to the urinary tract and no history of urinary tract disease. Their ages ranged from 6 weeks to 14 years. There were 124 uncircumcised boys with a mean age of 4·8 years and 60 circumcised boys with a mean age of 6·7 years. None were receiving or had recently received an antibiotic and none were on any immunosuppressive treatment.

Sampling was as follows: in the uncircumcised boys the preputial sac was sampled In the circumcised a swab was pressed against the periurethral area and the urethral meatus In both cases a moistened swab was used. The swab was then inserted into Amies transport media and sent promptly to the laboratory where blood agar, McConkey's agar, and neomycin blood agar were inoculated and incubated for 48 hours in aerobic and anaerobic conditions and the isolates identified and recorded.

Results

The results are shown in table 1. They show a significantly higher rate of *P mirabilis* in uncircum-

Table 2 *Isolation of organisms from uncircumcised boys in different age groups*

Organism	*No (%) of boys in age groups*		
	6 weeks–<1 year (n=27)	*1–<5 years (n=32)*	*5–14 years (n=65)*
Proteus mirabilis	12 (44·4)	8 (25 0)	8 (12·3)
Streptococci	1 (3·7)	0	5 (7 7)
Escherichia coli	4 (14 8)	0	1 (1 5)
Staphylococcus aureus	1 (3 7)	0	0
Bacteroides	0	0	1 (1 5)
Commensals/no growth	12 (44 4)	24 (75 0)	51 (78 5)

cised boys (22·6%) compared with circumcised boys (1·7%) ($p<0·001$)

Table 2 shows a breakdown of the figures according to different age groups The figures sometimes add up to more than the total number of patients as in some cases a mixed growth was reported—for example, proteus and streptococci. There was a decreasing incidence of proteus isolation with age in uncircumcised boys ranging from 44·4% in infants, 25% in the 1–5 year olds, to 12·3% in school age children. These differences are significant ($p<0·001$).

Growths of proteus in uncircumcised boys were reported as heavy in seven patients, moderate in 11, and light in 10. The heavy growths occurred only in infants and preschool children.

The one swab from a circumcised boy to grow proteus had a mixed culture with only a light growth of proteus. As so few circumcised boys had positive cultures, analysis by age group was not possible

Discussion

Hallett *et al* showed that proteus was a common cause of urinary tract infection in boys and was responsible for 67% of infections in their series.[1] They produced evidence suggesting that the organism might originate from the prepuce or urethra

The same authors isolated proteus from preputial swabs in 82% of boys who had had urinary tract infections; they found proteus in only 10% of a control group of boys and all of these were under 6 years of age As mentioned above we also isolated proteus much more commonly in children under 5 years old and only obtained heavy growths of the organism in this age group.

Hallett *et al* also showed that the pattern of infecting organisms changes at puberty and that *Escherichia coli* becomes the predominant organism in adult males,[1] although over the age of 60 years proteus again becomes a frequent pathogen suggesting a relation to prostatic secretion.

Clearly simple carriage in the preputial sac does not always lead to urinary tract infection.

In patients with urinary tract abnormalities and those who get repeated attacks of urinary tract infection *P mirabilis* is an important pathogen frequently affecting the upper urinary tract. No 'clear' virulence factor has been shown to be important. There is no relation between the organism's adhesiveness, origin, and its association with urinary tract infection [2] It would be of interest, however, to study preputial strains in subjects who develop urinary tract infections and compare them with simple carriers.

A recent study in infants by Wiswell *et al* showed that the declining frequency of routine circumcision was accompanied by an increased incidence of urinary tract infections [4] They considered only infants and did not record any causative organisms.[4]

It would be difficult to justify routine circumcision If one regards the incidence of urinary tract infection in boys of all ages as 0·9%, circumcision might protect four or five boys per 1000 from proteus species. This hardly seems justifiable bearing in mind that the operation is not without risk Alternatively some form of foreskin cleansing might be an alternative approach to prophylaxis, but it is rarely practised.[5]

Ghazalis *et al* have shown the close relation between urinary calculi and proteus infection so these infections must be taken seriously.[6]

We consider that this study strongly points to the preputial sac as an important reservoir of *P mirabilis* in the age group investigated. Study of the virulence factors of different strains may give an indication of those that will invade the urinary tract.

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Accepted 7 December 1987

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An unusual case of pycnodysostosis

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SUMMARY A 6 year old boy with clinical and radiological features of pycnodysostosis is described. In addition to pycnodysostosis he had a myelophthisic type of anaemia suggesting an overlap with osteopetrosis.

The term pycnodysostosis was coined in 1962 by Maroteux and Lamy who reported certain consistent variations in the syndromes of osteopetrosis and cleidocranial dysostosis.[1] Altogether, a total of 77 cases have been described The syndrome has been seen in individuals of many races and nationalities including black, Arab, and white.[1] The present case, reported from Lucknow, India has certain uncommon features.

Case report

A 6 year old boy was brought to the childrens' outpatient department with complaints of a large head and protuberant eyes that had been worrying his parents over the last several months. There were no other important symptoms. He had, however, been admitted to hospital at the age of 4 months when his limbs were noted to be excessively curved. Multiple fractures of the long bones and blue sclerae had been detected at that time and he was discharged with the diagnosis of osteogenesis imperfecta. Since discharge he had remained well.

He was the third child born of a consanguineous Muslim marriage. The other siblings were normal and no other family member had repeated fractures or an abnormal facial appearance. His father had a malformed, hypoplastic pinna on one side. On examination his weight and height were 14 kg and 87 cm, respectively. He was pale. The head appeared large with frontal and parietal bossing, a wide anterior fontanelle (4×4 cm in size) and open cranial sutures. The eyes were protuberant and sclerae appeared blue. Fundus examination was normal The hands were short and broad with dystrophic nails. There was bilateral anterior bowing of the tibiae. The liver and spleen were felt 4 cm and 2·5 cm below the costal margin, respectively.

Investigations showed a normocytic, normochromic anaemia with a haemoglobin of 55 g/l on admission. Reticulocyte count was 2%. Serum calcium and phosphorus concentrations and alkaline phosphatase activity were within normal limits. Radiographs showed a generalised increase in bone density. The skull showed wide open anterior fontanelle and sutures, especially the parieto-occipital. The mandibular angle was obtuse so as to be almost obliterated. Metaphyseal striations in the long bones were not seen. The distal phalanges of the fingers were tapering with absence of the ungual tufts. Bone marrow aspirate was difficult to obtain because of hard bone that was difficult to pierce but a trephine biopsy specimen showed few bony trabeculae and a fibrosed marrow space. A computed tomogram of the head gave a normal result.

Discussion

Pycnodysostosis may be recognised at any age from infancy to adulthood. Clinical features are short stature at all ages, fractures, large head with frontal and parietal bossing, open anterior fontanelle and cranial sutures, obtuse mandibular angle, prominent eyes with bluish sclerae, underdeveloped facial bones, persistence of deciduous teeth into adulthood often with caries, short, broad hands and feet with dystrophic nails and trunk deformities such as kyphosis, scoliosis, increased lumbar lordosis, and narrow chest.[2]

Laboratory investigations usually give results within normal limits. Raised plasma calcitonin concentrations have been reported, however.[3] A generalised increase in bone density is seen on radiographs, but medullary canals are evident. Some degree of widening of the distal femur may be seen. The skull shows open anterior fontanelle and sutures with small facial bones, non-pneumatised paranasal sinuses and a flattened mandibular angle. A wormian bone pattern may be seen in the parietal bone. Terminal phalanges in the hand are partially or totally aplastic with loss of ungual tufts. The acromial ends of the clavicles may also be aplastic Other abnormalities include failure of complete segmentation of the atlas, axis, and the lower lumbar spine, coxa valga and abnormal radioulnar articulation.[1] Histologically, the appearance is similar to that of osteopetrosis but the medullary canals are present and microscopic evidence of haemopoiesis. A dynamic study of tetracycline uptake led to the conclusion that there is a slowing down of bone resorption and formation.[4]

An autosomal recessive pattern of inheritance of pycnodysostosis is suggested. Elmore *et al* reported a deletion of the short arm of chromosome 22 in a patient and several unaffected family members.[5] This suggests the possibility that the gene is located on the short arm of this chromosome and that it manifested itself in the hemizygote state in this patient.

Features which differentiate osteopetrosis (Albers-Schönberg disease) from pycnodysostosis are normal stature, cranial nerve compression, myelophthisic anaemia, osteitis, non-differentiation of cortex from medulla in long bones, more severe modelling defect, and an appearance of alternate radiodense and lucent bands (striations) near the metaphyseal ends of long bones in the former. Biochemical abnormalities such as raised serum alkaline phosphatase activity are also seen. Skull dysplasia, blue sclerae, and hypoplasia of the distal phalanges are not commonly reported with osteopetrosis.[1]

The patient described here had the clinical and radiological features of pycnodysostosis. In addition he had a myelophthisic anaemia with hepatosplenomegaly, which is not commonly reported in this disorder and in fact is held to be a differentiating feature separating it from osteopetrosis [1] Similar cases have, however, been reported.[6] The disorders osteopetrosis and pycnodysostosis may represent the two ends of a spectrum, so that an occasional patient has overlapping manifestations of both. This patient therefore reinforces the belief that a close relation exists between these disorders.

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Accepted 22 December 1987

Archives of Disease in Childhood, 1988, **63,** 560–564

Current topic

'. . . . officiously to keep alive'

C H M WALKER

Perth

Modern medical technology has provided powerful tools with which to initiate and sustain life and understandable concern is being expressed about scientists and doctors 'playing God.' The view that 'the clinician's freedom to stop intensive treatment when the probable outcome is severe handicap is part of the package of neonatology'[1] is far from unanimous. The hard facts are, however, that today up to 30% of deaths in a neonatal intensive care unit may follow deliberate withdrawal of life support[2] and despite concern for more than a decade[3] the ethics of this issue are still sub judice.

The questions

Who is to say that procedures such as AID (artificial insemination by donor), IVF (in vitro fertilisation), or surrogacy are right or wrong? Who knows the wisdom or folly of saving the lives of thousands, even millions, who mankind cannot, or is not prepared to feed? How long should we live 'aged and infirm'?

Not the least of these weighty questions is that of the justification of termination of life support in the newborn. While some advocate preservation of life at almost any cost others believe there is a time when 'enough is enough'. But who decides? Some claim that not to try to preserve life is defeatist, denying progress, and morally wrong, yet by our interference with what might be regarded as a 'natural selection' are we creating more problems than we are solving? As with atomic energy, has society again been guilty of accepting the use of new procedures before either considering adequately the circumstances in which they should be used or the ethics of their use?[4] While everyone would agree that mortality statistics should never influence the initiation, continuation, or withdrawal of medical treatment, what of family disruption, availability of resources, cost effectiveness, and even the law?[5] The magnitude of these dilemmas and the interest they engender is illustrated by the fact that the whole of the June 1987 issue of *Clinics in Perinatology* is devoted to ethical and legal issues in that specialty.

Ethics

With the exception of some forms of gross congenital deformity those attending a delivery *are now obliged* to resuscitate virtually all infants born around 22–24 or more weeks' gestation The frontier for survival has crept steadily down from 1000 g to 600 g birth weight over the past 10 years, though this of course is modified by the local facilities available. It no longer seems justifiable, therefore, to withhold this care purely on the grounds of gestational age or birth weight, or both, as babies of about this maturity survive at birth with assistance and can, though not always, grow up to be normal children [4 6] But for those lives already established and being maintained artificially the decision to withdraw life support is more complex. To adopt the 'near certain death or no meaningful life' criteria[2] is a helpful approach for some, maybe for many, but there remain those for whom life in almost any form is sacred Even the more radical views of the Roman Catholic Church leave room for judgment when it comes to using 'extraordinary means' to preserve life or where 'a technique carries a risk or is burdensome in the light of likely benefit.'[7] Both the patient and others may be considered in this context and we are hearing a great deal more today about the 'unremitting burden on carers'.[8] This presumes, however, that the newborn, not yet being a 'person' does not have similar rights to those of children and adults,[1 9] an assumption also challenged by all those who believe life and rights begin at birth, the age of viability, or even at conception

Be this as it may it is surely acceptable to discontinue support when for a number of weeks, and it usually takes this long to be certain, a child has shown no potential for recovery and when sustaining life is merely prolonging the distress for parents and carers alike. It is of course wrong to assume that continued intervention can cause no harm (an important ethical principle) as the complications of some life support measures are certainly harmful and the risk of trauma and/or other pathology may well increase with the duration of treatment. On the other hand, decisions to discontinue support are now strongly influenced by prediction, albeit imprecise, of the quality of future life While prognosis is now reasonably accurate,[10 11] and will undoubtedly improve with future long term follow up data. the important question remains—is it better to be dead than handicapped?[12]

Predictions

Before any decisions are made it is paramount that parents are given adequate and if need be repeated explanations of the medical problems, current and future. Breaking bad news is never easy but it pays to be gentle but frank and hope to win the parents' trust about keeping them fully informed as to how the baby is progressing. It should be made clear that, despite all the technology and knowledge available, neither of the two principal indicators for the withdrawal of life support—near certain death and survival with severe handicap—can be foreseen with absolute certainty.

It has been suggested that there are 'clinical categories' for stopping treatment—severe asphyxia, preterm infants with major intraventricular haemorrhage, uncontrollable convulsions, and certain syndromes[13]—but these cannot in themselves consititute criteria. One recent study showed that even using significant predictors as indices, there was an error rate of at least 20% when attempts were made within 24 hours of birth to predict survival in infants less than 801 g [14] Thus, with a few exceptions, the decisions about continuing intensive care should not be made until there has been a period of assessment and preparation. How long this should be depends on the individual case but in most instances this is measured in weeks rather than days.

The easy predictions are those where the baby has one of the readily recognisable congenital syndromes which are always associated with lethal anomaly or severe mental retardation, or both In such cases primary resuscitation and life support are usually withheld from the outset. Syndromes with lesser and doubtful degrees of disability and those with acquired lesions leading to handicap pose more difficult problems which not infrequently resolve into an estimate of the degree of permanent damage.

There are as yet no established criteria of brain death in the newborn as those generally accepted in the adult are not applicable. Death can be anticipated with reasonable confidence, however, when brain injury is so extensive that the pupils are fixed, where there is evidence of cerebral atrophy and failure of head growth, and the electroencephalogram shows no activity even on maximum stimulation. Serial tracings showing progressive deterioration are helpful[13] but the electroencephalogram is difficult to interpret in the newborn, especially if barbiturates have been given, and is even less reliable in the preterm infant. Death can also be anticipated when extensive lung damage is such that there is total dependency on a ventilator and where progressive increase in ventilation oxygen and pressure are causing further pathology. It can also be anticipated when lung destruction is associated with progressive and intractable respiratory failure or cor pulmonale. While it is alsc more likely in the presence of intractable renal failure or other severe metabolic imbalance, or both, these are, to some extent at least, correctable and are not good predictors Hypothermia and sclerema, once thought to be 'terminal' and fused eyelids, once thought to indicate previability, do not, with modern treatment, indicate early demise.

Assessment of the extent of brain damage and its relation to future handicap is becoming rapidly more accurate as, in skilled hands, the various types of scanning image now correlate well with necropsy findings. Extension of intraventricular haemorrhage into the cortex and bilateral periventricular leucomalacia are usually associated with severe degrees of handicap, though such an outcome does not necessarily follow intraventricular haemorrhage or ventricular dilatation. Less precise still are the predictions about the long term effects of cerebral oedema or imbalance of glucose, sodium, and other electrolytes. The value of enzyme assay, brain stem evoked responses,[13] and carotid artery flow measurements as predictors of severe permanent brain damage and handicap have yet to be fully clarified but so far none have shown great promise.

'When in doubt—don't!' may seem a crude philosophy in this situation but while doubts about the life and the extent of damage in survivors should be admitted and discussed with the parents they should preclude any mention of withdrawal of treatment until they have been resolved sufficiently for the caring team to reach a decision among themselves.

Medical and nursing staff must realise, however, that parental understanding of the full impact of the situation after the first or even further consultations may be negligible. The skill is in the recognition of the parent(s) who take in the implications of what has been said and those who block them or fail to grasp the situation. Only when the caring team feel they really understand, or understand as much as they ever will, should the possibility and timing of withdrawing life support be discussed.

No matter what the doubts and uncertainties that doctors may still have about the likelihood of death and/or handicap they must, having made a decision with their team as to what they believe to be in the best interests of the baby and family, give positive, unequivocal, and convincing advice to the parents.

It should be explained that on withdrawal of the ventilator the baby may go on gasping for a little while and that, rarely, the baby may establish respirations and survive. While the latter possibility should be mentioned, too much should not be made of it lest parents raise too many false hopes. In the event of unexpected survival there is no virtue in the doctor doing anything but admit he did not expect the baby to manage on his or her own, and for those doctors and parents with a religious faith comfort is to be found in the belief that the baby was perhaps just 'meant to live' no matter what the future holds. Parents must of course be reassured immediately about the support they will receive in the event of long term survival with handicap

Decisions

Once the team feel that the period of discussion and explanation has been adequate and that the parents are ready to face the prospect of the death of their baby the possibility of turning off the ventilator can be raised. The parents should be told that the team feel the time has come to 'let nature take its course,' that everything possible has been done for as long as is necessary to know that the baby has little or no chance of survival let alone of having a happy even near normal life. Eventually the question should be put as to whether the parents would consider such a step yet or would they prefer to continue the ventilation for a little longer.

Opinion as to who should make the final decision to terminate treatment seems to vary [15] Some professionals think that after adequate discussion and counselling the parents should make the decision Some parents feel they have this right and wish to exert it while others thought in retrospect that they had made the decision when in fact they had merely accepted the doctor s advice.[13] Others would go so far as to say that it is 'intolerable for parents to have to be responsible for such decisions' and as it is the doctors who understand the risks and limitations of intensive care procedures it is they who must be responsible for their initiation and withdrawal.[16] I believe that it is better, after unhurried consideration by a group comprising parents, nursing staff, family doctor, social workers and, if the parents so wish someone from the chaplaincy, for the doctor to make the concluding suggestion that it is timely to withdraw support and invite the parents to agree or disagree. In this way the parents are to some extent relieved of the possible distress of, at a later date, regretting that they alone had decided to let their baby die. Is it not better to have them remember the discussion team making the overture, their own part being that of taking the best advice available at the time?

Should the parents wish treatment continued then the decision is, for the time being at least, easy but another opinion should be procurable and offered if they show the least signs of uncertainty about the advice being given. Whether this should be consultation with another similar but clinically uninvolved group or a formal bioethics committee is a matter for local arrangement [4 17] While rigid rules for decision making in this situation are quite inappropriate conclusions should nonetheless be reached in the open and without coercion or conspiracy [4]

Preparation for loss

Preparation for the event of death eases the blow when it comes and the rational participation of parents in decision making is possible despite their grief.[18] Paediatricians are sometimes reluctant or feel unable to discuss life and death or life hereafter[19] but no matter what their own beliefs may be they should have someone on their team who can talk with parents about these matters before and after the event of the death of their baby. While doctors can usually explain the mechanism of death these other and fundamental questions still remain unanswered and what the medical and nursing staff think about such matters personally is irrelevant. The questions such as 'Why us?', 'Why our baby?' are unanswerable but some parents find solace in the belief that God has a plan which they may not understand but which their faith helps them to accept

Sometimes the parents ask for treatment to be stopped and they may do this too early or quite inappropriately. They don't think of this as killing, although of course there are members of our society who do. On the one hand it is understandable that parents cannot stand the strain of waiting for the unknown; the days, weeks, or even months of not knowing if they will in the end have a live baby. Some don't want to face the risk of the survival of an abnormal child and a few just didn't want the baby in the first place—and still don't On the other hand most will leave no stone unturned before reaching the painful decision to agree to termination of care. It must be a rare event indeed that life support is terminated inappropriately early or without due consideration, but unfortunately there are clandestine groups of which paediatricians have become only too aware who are eager to report clinical action of this nature to the police if they think it is contrary to their beliefs.

Nowadays most parents, usually the mothers, wish to hold their babies at the time of withdrawal of life support, being assured that at no time is care in the form of warmth, comfort, control of pain, and nutrition withheld There should be sensitive and unhurried discussion about this event and about arranging the 'last rites', family visits, final photographs, and other practical details before action is taken. Parents should have no anxieties caused by lack of knowledge of what happens to the baby's body, how they contact the undertaker and what it is all going to cost—factors which caring teams have in the past tended to neglect.

Each case is unique and must be treated as such and the decision to terminate care influenced mainly by the moral and ethical codes of the society and the parents involved. The parents should of course be invited, but not pressurised, to return in a few weeks for a further discussion about the causes of death and the necropsy results and to discuss with the obstetrician the prospects for future pregnancies

The future

With rare exceptions initial resuscitation is advisable as this gives valuable time to make detailed clinical assessments and to prepare the family for their loss Long term developmental studies will provide yet more accurate information about prognosis after threatening episodes such as intraventricular haemorrhage, leucomalacia, convulsions, and metabolic imbalance. As predictions about an infant's future capabilities improve so will the medical attendant have greater confidence in the advice offered.

The final hurdle, however, is to obtain 'permission' from society for the medical profession to adopt some code of practice which will give the paediatrician confidence that if and when support is discontinued after an approved procedure involving a period of medical treatment and joint consultation he will not be under threat of fiscal action.

The arguments as to whether there is any moral difference between 'killing' and 'allowing to die' have little relevance as there is already a widespread though not total social acceptance of the latter for which criteria of moral justification and legal acceptability are still required.[9] As Dame Mary Warnock puts it '. . . doctors ought to be given a general rule for the management of ill babies.'[16]

A start has been made to provide the profession with guidelines for protection in law in the form of an independently proposed 'Draft Limitations of Treatment Bill.'[20] This outlines the circumstances under which it would *not* be an offence to withhold or withdraw treatment in the newborn. Some of the provisions include, for example, that the infant should be under 28 days of age; that parents have given written consent; two doctors (one a paediatrician) of not less than seven years standing willingly give a written statement as to the medical status of the baby—for example, the irreversible nature of the condition or unavailability of further treatment, the expected quality of life, taking into account the pain and suffering of prolonging treatment—for example, repeated surgery—the attitude of and effects of prolonging care on the family, and the willingness and ability of the family to provide long term support in the event of handicap. Food and sustenance would, however, be continued unless its provision would directly increase the degree of pain and suffering. The fact that this draft bill has not so far been taken up either by the government or any member of parliament as a private members bill raises a number of questions. Are paediatricians considered as already acting with sufficient expertise, wisdom, and good faith that no change in the law is required? Is what the caring teams are doing acceptable even though they are regarded by some as immoral and unethical and skirting the edge of the law? Do the law makers support the belief that to legislate would set arbitrary or even unworkable rules which could make things more difficult for the profession rather than less?[21] Or is it that there is so much difference of opinion that they believe it to be virtually impossible to formulate policies which would satisfy a majority?

Meantime the paediatrician caring for the newborn is caught in the middle—damned by some if he does preserve life, accused of enthusiastically using his high technology regardless of the quality of life preserved, and damned by others if he doesn't, branded as guilty of euthanasia or even murder—in limbo, encouraged by the majority of society, but unprotected by the law.

The Bioethics Committee of the Canadian Paediatric Society has proposed criteria which forbid hastening death in any way but consider withholding care if (a) there is irreversible progress of disease or imminent death; (b) treatment will be ineffective or harmful; (c) life will be short, even with treatment and where nontreatment will permit more comfort and caring; and (d) future life will entail intolerable pain and suffering. Other, though very similar, guidelines have been suggested in the United States[13 22] and now in the United Kingdom[20] but in the end the criteria are established and the clinical decisions are made locally in the light of the circumstances of each individual case with the careful balance of potential immediate and long term risk against potential survival and lifestyle I believe that ethical committees should not take part in what is a very complex but personal decision but have a watchdog role and be called upon in the event of indecision or dispute. Precise regulations are unlikely to be sufficiently flexible for these multifaceted and highly individualised situations and many will share the concern over the restrictions which legislation might impose.[21] It is surely timely, however, for doctors and lawyers together to pursue, though not necessarily in haste, the composition of a generally acceptable code of conduct for the guidance of both professions

For example:

(1) The caring team should consider the case in the light of the four criteria proposed by the Canadian Paediatric Society (above).

(2) A second doctor (consultant paediatrician or principal in general practice) should agree to and cosign a statement describing the clinical status of the baby and the reasons for recommending withdrawal of care.

(3) After preparatory talks and when the caring team regard the parents are ready a case conference should be held involving the parents, caring team, family doctor, social worker, and if desired by the parents a member of the chaplaincy at which these circumstances (see (2) above) are explained and withdrawal of care is suggested to the parents.

(4) If they agree, this is minuted and signed by the conference leader. (Parents should not be asked to sign as this is distressful and there is no need when their agreement is witnessed by so many people and documented.) A smaller, less formal and more intimate meeting to describe what actually happens and to learn what the parents would like to happen is planned to follow as soon as possible.

(5) If they are unsure or disagree, treatment is continued and another medical opinion is offered.

Though such guidelines have no legal standing they could at least give doctors a set of general ground rules concerning the process which should be followed before, during and after withdrawing intensive care and give the lawyers a similar guide as to what they consider should have been done in the event of cases coming to court. This common understanding could perhaps give paediatricians a degree of protection from the crossfire to which they are currently exposed and go some way towards smoothing if not completely calming these troubled waters.

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Archives of Disease in Childhood, 1988, **63,** 565–566

Commentary

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Dr Colin Walker has discussed, with sensitivity and admirable objectivity, some of the difficult questions that have dominated the ethics of infant care since the 1960s. Neonatal intensive care has been remarkably successful in ensuring the healthy survival of smaller and smaller infants and in preventing a considerable amount of crippling disability In acknowledging its triumphs, however, we must not ignore its disasters—infants kept alive through the indiscriminate use of life saving techniques and condemned to 'lives' of grievous mental and physical handicap at great cost to themselves, their parents, and to society. During the past two decades the issues have become even more complex. Debates on the treatment of individual infants have become public, and paediatricians have found themselves in conflict with individuals or groups who have no connection with the infants or families concerned. Conflicts arise more from differing moral views about life and death or from differing interpretations of the law than from disagreements about the diagnosis or prognosis Discussions and decisions previously viewed as intensely private matters between doctors and parents increasingly are subject to legal scrutiny and even, as in the United States, to government legislation.

An important question not addressed in detail relates to the advisability of resuscitation *at birth* of infants born at the limits of viability or with obvious severe abnormalities. Occasionally such an infant will do remarkably well but resuscitation may result in only a brief period of survival perhaps maintained by further intensive care or it may ensure more prolonged survival but with the infant's future clouded by grievous handicap—what Rachels calls 'being alive' as distinct from 'having a life '[1]

Dr Walker states that 'with rare exceptions initial resuscitation is advisable as this give valuable time to make detailed clinical assessments and to prepare the family for their loss.' I agree. The delivery room is no place for 'snap judgments' of this kind especially as those responsible for taking immediate decisions about resuscitation may be relatively junior and may not have access to all the information Inevitably too, there will be some uncertainty about the prognosis especially for the very tiny infants born at gestational ages under 26 weeks, some of which show remarkable vigour at birth and deserve a 'trial of life.'

It is important that junior doctors be given clear instructions about their responsibility regarding neonatal resuscitation. Infants of whatever gestational age or whatever the apparent abnormality should receive standard resuscitation including intubation and intermittent positive pressure ventilation if necessary when signs of life (respiratory effort or heartbeat) are present at birth. Subsequent decisions about the introduction or continuation of intensive care procedures to maintain life will be the responsibility of a senior doctor, usually the consultant, after discussion with the parents and other specialist colleagues as indicated.

Dr Walker is not specific about the 'rare exceptions.' It is difficult to list examples of congenital abnormality for which resuscitation is inappropriate because there is so much variation in complexity, severity, and prognosis. Much also depends on the attitude of the parents and the staff immediately concerned. It is worth recalling that the incidence of stillborn infants with spina bifida dropped significantly in the early 1960s after the introduction of a more optimistic surgical approach to treatment.[2] Anencephaly and similar gross abnormalities of brain development are perhaps the obvious exceptions to the general rule regarding resuscitation. With modern imaging and other techniques of prenatal diagnosis most of these infants are now identified during pregnancy and discussion with the parents should include consideration of the appropriate care at birth. In these circumstances there is no justification for employing intensive care in futile attempts at prolonging life. Nevertheless these infants deserve our respect as human beings no less than others and should be given all basic care with relief of any apparent distress of discomfort until they die. There have been suggestions that they could be valuable sources of organs for transplantation and might be kept alive until recipients are identified. Such a practice would conflict with some basic tenets of medical ethics and has disturbing implications if extended to other areas of clinical practice.

For the very tiny infant I believe that the decision on resuscitation in the delivery room is relatively straightforward *All* infants showing signs of life should be resuscitated using intubation and intermittent positive pressure ventilation if necessary. What happens after the infant is transferred to the intensive care nursery is another matter. Previously, I have identified some infants who should not receive intensive care and have suggested a flexible cut-off weight of 750 g at appropriate gestational age below which assisted ventilation would not be introduced *routinely*[3] Paediatricians working in neonatal units have widely varying personal views on the appropriate use of intensive care for these very tiny infants. How selectively or how indiscriminately paediatricians use their skills and technology to prolong life should be the subject of continuing debate. Inevitably the criteria will continue to change. We must consider not only the effects of current practices on the infants themselves but the views of parents who must live with the consequences. We also must recognise the effect on resources that might otherwise be deployed elsewhere.

An exception to the above general rule is the tiny infant born with signs of life after an attempted late termination of pregnancy.[4] Paediatricians may be asked to resuscitate and treat one of these tiny abortuses despite the fact that a few minutes earlier, a gynaecological colleague was attempting to kill it. At present the law confers protection on every infant born alive and paediatricians have a duty to care for them but these infants may be damaged during the abortion procedure and are likely to be hypoxic, acidotic, and hypothermic by the time paediatric assistance is requested. It is also unlikely that their mothers will wish to care for them. Pressures to provide aggressive resuscitation and intensive care for these infants should be resisted.

To withdraw or withold a life saving treatment such as intermittent positive pressure ventilation from an infant is always a difficult and often an agonising decision to take but it is one which sometimes must be faced in the interests of infants and families It is important that such a decision is made on good medical grounds based on an accurate diagnosis and prognosis. In future years economic considerations increasingly will affect decisions that utilise expensive high techology medicine With finite resources and apparently infinite demands for care a 'line' must be drawn somewhere. Neonatal intensive care, which has expanded so rapidly in the past few decades cannot escape such constraints. We should ensure that this 'line' is drawn by paediatricians acting in the best interests of their infant patients and not by those responsible for the control of hospital budgets.

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Personal view

Why irritated?

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The Editor, by asking me to write this article, reminded me of many of my past sins and alerted me to the danger that I would give the impression that my management of patients was always impeccable—and that would be very far from the truth. Someone once said that as one gets older, one makes all the old mistakes with ever increasing confidence. I would like to think that as one gets older one becomes more tolerant of man's foibles and feels less irritated by them—or at least conceals it. I believe that we should consider what irritates, why it irritates, and what we should do about it.

Infants and toddlers do not irritate, but the older preschool child (or his older sibling) may—because of his disruptive, unchecked rampaging round the room, his violent struggling when his mother is trying to give him three drops of polio vaccine, or his screaming and fighting when his mother tries to bare an arm for his diphtheria tetanus injection. Less often the child strongly resists the physical examination, and with great effort one represses an almost overwhelming urge to smack his bottom

Why does all this irritate? Perhaps because of one's own impatient and intolerant personality, or because of pressure of work, fatigue, or an overdue mealtime. One forgets that the child, too, may be tired, hypoglycaemic, hungry, unwell, or that especially after an accident, he is afraid of the unknown. He may have had an unpleasant experience in hospital or at the hands of a doctor, with nothing more than a clumsy examination of his throat. His behaviour reflects management at home, lack of loving discipline, or threats that if he does not eat his dinner he will be taken to the doctor. In a 36 page chapter, entitled the Basis of Behaviour, and in chapters on individual behaviour problems, I tried to summarise the origins of children's behaviour.[1]

There is no easy way of dealing with the problem. One talks to the child and keeps on talking to him—and gets the mother to do the same—in order to distract him from his fears.[2] Where possible I talk to the child first—before eliciting the history If that fails, it is best to leave the child for a while to thaw out while one talks to the mother. If he does not want to lie down on the couch, one gets the mother to lie him down—and if necessary examines him in the kneeling position. If he is afraid of having his throat examined, he may press the tongue down himself—and one leaves the throat examination to the last.

Why does a mother irritate one? It is difficult to avoid feeling irritated when a mother or father says 'I don't believe in immunisation,' or excuses her failure to bring the boy for his second diphtheria, tetanus, pertussis vaccination until a year or two after the first, by saying that 'he's had a cold all the time' and expecting the doctor to believe it (because he looks stupid and gullible). When her 4½ year old is brought for his diphtheria tetanus polio booster, she warns him of his impending agony by saying 'Try to be brave—and I'll give you a sweetie.' She says that her 7 year old girl is 'very delicate—she's so sensitive, and I'm afraid that she's outgrowing her strength.' In front of a 10 year old girl she says 'She's always been a big disappointment to us, She's not nearly as clever as her brother.' After an hour's session with the doctor, during which she described innumerable symptoms suffered by her child, none of them suggesting disease, she goes away and complains that 'I've never been told a thing.' She had not liked to express her real fear—that her child has leukaemia, like a neighbour's child, and the doctor had failed to realise that she had not told him about her real fear

In a busy accident and emergency department the hard pressed doctor, tired after a disturbed night, or a succession of severely ill children, finds it hard to be patient with an aggressive mother who demands to be seen out of turn, or be treated privately: she is going to Majorca tomorrow and wants to be sure that her boy's knee, grazed a week ago, has healed, so that he can swim there—or at least go through the motions, as they say It is hard for the doctor to be kind and sympathetic to a mother with her child who has a 'non-accidental injury'—not realising that the mother suffered in the same way as a child, with punitive non-loving parents, and that she has dreadful problems without a home of her own, with overcrowding, massive debts, a mentally subnormal older child who cries constantly, wets and soils, and will not sleep. She is battered by her alcoholic cohabitee, is worn out, anaemic, bored, and with absolutely no hope for the future. The next patient has trapped his finger, and his mother is aggressive, because she is in a panic and feels terrible guilt for allowing the accident to happen.

A grandmother may irritate too, when she accompanies her daughter, and will not let her give the history herself.

It is essential never to appear to criticise a mother for her child's difficult behaviour. She has done her best but has had conflicting advice from relatives, doctors, books and journals. It is important to let her talk: many a mother has complained that it is no use talking to her doctor, for he 'just won't listen' But it is not enough just to listen: one has to try to allay her anxieties and worries.

When a mother has been irritated by another doctor, one has to use all one's tact to cope with the situation. Scores of mothers have expressed to me their irritation at being told that they are 'just overanxious, imagining things,' or 'fussing about nothing. The mother may or may not be telling the truth, but one can say with certainty that it is dangerous in the extreme to discard a mother's fears if she is insistent that there is something wrong with her child. I told all my students never to use those words when speaking to a mother: a good mother *is* anxious about her child—especially if he is an only one.

It may be difficult for one to avoid feeling somewhat irritated by another doctor's treatment, and not to feel disturbed if a doctor seems to have allowed medical etiquette, with regard to his colleagues, to override the interests of his patient, which should always be paramount. For instance, it can never be right for a consultant to operate on a child (for example, for tonsils), not because it is in the child's best interests, but because he wants to please the family doctor who recommended it or just to please the parents.

I feel disturbed when a family doctor or consultant refuses to allow a mother to obtain a second opinion. She has every right to, but it is a strange and irrational fact that when a second opinion is sought (or a test is repeated) the second one is accepted as correct. If a mother asks for one's opinion after consulting someone else, one has to give it—and one certainly has to express disagreement with a previous opinion if one feels that the treatment was potentially harmful or that the operation recommended was unnecessary.

One may feel irritated by a child, his parents, the granny, or his family doctor—and the mother may be irritated by the doctor. After a busy outpatient or child health clinic I have often felt irritated with myself—feeling that I may have appeared to criticise a mother when she was seeking advice, or have failed to deal adequately with her questions and anxieties, or have managed a resistant preschool child badly—and annoyed because I realise that with pressure of work I have forgotten to write down some important physical signs.

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Archives of Disease in Childhood, 1988, **63**, 569–575

Correspondence

When not to do a lumbar puncture

Sir,

Although an important point is made that a lumbar puncture may not be the essential first investigation for a very sick child who may have meningitis, I think there are some points in Dr Addy's annotation which deserve further discussion [1] I think it is unfortunate to use the word 'assault' about this investigation Also the fact that cerebral oedema and 'coning' are quite commonly found in children dying of meningitis does not necessarily indicate that lumbar puncture contributed to their death.

There are, I think, three different situations which this annotation is referring to and there are quite different reasons for omitting or deferring a lumbar puncture in each

(1) In, for example, a child with classical clinical presentation of meningococcal infection a lumbar puncture may be merely unnecessary and could delay, though of course should not, the first dose of antibiotic

(2) The child may be 'too sick for lumbar puncture ' This, I think, is the main point of the article I think it may be clearer to say that, for a child in coma, there are priorities in resuscitation and investigation which may cause one to defer a lumbar puncture until problems of underventilation, status epilepticus, circulatory failure, and hyperpyrexia have been dealt with There can be no doubt that dealing with underventilation and presumed cerebral oedema are much more important Very often it takes only about half an hour to have either completed the above or at least to have made progress, and a lumbar puncture may then be safely performed There is absolutely no reason why antibiotics should not be given for presumed meningitis at the outset of resuscitation If the child's depth of coma warrants this, then intracranial pressure monitoring by an intraventricular drain does, of course, provide cerebrospinal fluid as well

As an additional point about cause of death, it has been our experience that, in children with overwhelming infection, a major problem has often been failure of adequate cardiac output, which fails to respond to drug treatment or our efforts at minimising the effects of cerebral oedema

(3) The danger of delay in the diagnosis of other conditions is another consideration We see a large number of children with conditions which have been suspected of being meningitis, including tumours, abscesses, vascular episodes, and unusual presentations of epilepsy, in which the lumbar puncture is decisive in early referral One could say that the lumbar puncture was a mistake and that the children would have been better referred for an urgent computed tomogram I fear, however, that if the habit of not doing a lumbar puncture caught on, that a number of these children's diagnoses would be further delayed

Reference

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Sir,

We have followed the correspondence debating the need for lumbar puncture in the diagnosis and management of meningitis with interest, but wish to express our concern regarding the recent annotation on the subject.[1] Nowhere is consideration given to the difficulties surrounding the diagnosis of tuberculous meningitis In Third World countries tuberculous meningitis remains a commonly encountered form of meningitis in childhood[2,3] but the diagnosis should be considered at all times in every setting [4]

Early diagnosis is crucial, as the outcome is determined by the stage of the disease at which treatment is started [5] Many children show subtle premonitory symptoms before those of meningitis appear, and the clinician may be astute enough to perform a lumbar puncture at this optimal stage Other children, however, present acutely with a picture indistinguishable from meningitis due to other causes. Without a knowledge of the results of cerebrospinal fluid examination it is difficult to imagine how the clinician is going to consider the possibility of tuberculous meningitis in the differential diagnosis. A policy of diagnosing meningitis on clinical grounds, initiating meningitis treatment, and awaiting clinical improvement will be disastrous, if not fatal, in the case of this disease

It is true that in a minority of cases the presence of a strong family history, or a chest radiograph showing pulmonary tuberculous in the presence of typical neurological signs, enables a confident diagnosis to be made It is also true that when diagnostic uncertainty exists, computed tomography may assist the diagnosis of tuberculous meningitis by showing the characteristic basal exudate and associated hydrocephalus [6] In most countries where tuberculous meningitis is a common problem, however, facilities are limited, and even in developed countries a critical period may pass before computed tomography is undertaken

We would entirely agree that lumbar puncture is both dangerous and unnecessary in a child with meningococcal septicaemia, and in cases with definite signs of raised intracranial pressure But in developing countries, or in any country where tuberculous meningitis is still encountered, a policy of not carrying out lumbar puncture in cases of meningitis is in our opinion a recipe for disaster

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Correspondence now closed

Management of children with head injuries in district general hospitals

Sir,

In his paper on the 'management of children with head injuries in district general hospitals' Mr Hayward expresses the view that the primary responsibility for children with head injury should be undertaken by paediatricians [1] We agree with this opinion but would like to highlight that this does not appear to be current practice

We have just completed a survey of all children who were admitted with or who died from a head injury in the Northern Region between the years 1979 and 1987 In this period there were 25 152 such children of whom 258 (1%) died Thirty three children died at the site of the accident and a further 106 died on their way to hospital

Altogether 25 009 children were admitted to hospital, 10 5[illegible] (42%) of these children were admitted under the care of specialists other than a paediatrician or neurosurgeon. The number of children admitted to a regional hospital with expertise in both paediatrics and neurosurgery was 7179, and 6246 (87%) of these children were cared for by either a paediatrician or a neurosurgeon or there was shared care The number of children admitted to a district general hospital was 17 830, of whom 8202 (46%) were cared for by a paediatrician; 9628 (54%) of the children admitted to the district general hospitals were cared for by other specialists, primarily general or orthopaedic surgeons

Of the 116 children admitted to hospital and who subsequently died, 33 (28%) died at a district general hospital Twenty seven of these 33 children died under the care of a general or orthopaedic surgeon Twenty four of these 33 children survived more than six hours and could therefore have been transferred to a specialist centre

Head injury is the most common cause of death and acquired disability in childhood, yet there is no general agreement as to the most effective approach to either acute management or to rehabilitation The relative paucity of research into specific aspects of the management of children with head injury may in part reflect the present wide spread dispersal of the care of these children among different specialties

We agree with Mr Hayward that the high incidence of learning and behavioural difficulties which may follow even mild head injury[2] emphasises the importance of paediatric involvement in the acute and long term care of all head injured children even those with mild head injury

We believe that there is an urgent need for paediatricians to revise the facilities offered to children with head injury to ensure that they receive the highest standard of care Furthermore, research is needed in both the acute management of children after head injury and their rehabilitation in an attempt to reduce the high mortality and morbidity

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Tight nuchal cord and neonatal hypovolaemic shock

Sir,

Dr Vanhaesebrouck and his colleagues do well to warn of the danger of the hypovolaemic shock that may follow clamping and division of a nuchal umbilical cord.[1] During studies in Bristol (1963–5), it was observed that there was normally a shift in blood volume from the fetus to the placenta during the second stage of labour This 'feto-placental transfusion' was attributed to the more ready compression of the soft walled, low pressure umbilical vein than the firm, high pressure umbilical arteries, between the body of the fetus and the wall of the birth canal When the umbilical cord was clamped at the moment of birth, as much as 30–40% of the normal fetal blood volume might be trapped within the placental vasculature rendering the placental congested, tense, bulky, and more likely to be retained

On the other hand the newly born infant often exhibited transient signs of hypovolaemic shock with hypotension, tachycardia, and pallor due to peripheral vasoconstriction While this insult was tolerated remarkably well by most healthy term infants, it was capable of causing resuscitative and adaptive problems among those that were preterm, depressed or sick These observations were first reported in 1966–8[2] and have been reiterated many times since.[3] This hazard of immediate cord clamping, however, which may be largely obviated by a delay of 20–30 seconds, has been largely ignored by modern obstetric practice which is too often more interested in obtaining samples of umbilical arterial and venous blood between triple clamps than in understanding and preserving the normal physiology of childbirth [4] There is more excuse for division of a tight nuchal cord but when possible this is best avoided by unlooping the cord over the baby's head.

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Top up transfusions in neonates

Sir,

The article by Roberton on 'Top up transfusion in neonates' was both stimulating and provocative.[1] Comments about lack of cooperation of pathology services in neonatal intensive care units are common and highlight a growing problem which needs to be addressed

At present there are clear technical limits to reducing the quantity of blood required for most procedures The idea that appropriate ultra microscopic methods are likely to be available in the near future appears to be rather optimistic but much can still be done and the requirement for blood transfusion, with its known and unknown dangers, can be limited Dr Roberton did indeed refer to the problem of infants receiving blood infected with HIV in another Brisbane Hospital before the disease was recognised The Royal Women's Hospital in Brisbane which has approximately the same number of neonatal intensive care patients has a lower rate of blood transfusion and a similar epidemic did not occur here The reasons for the lower transfusion rate are not precisely known but include the following factors:

(1) A conservative requesting policy.
(2) A dedicated phlebotomy service. This ensures that the quality of the blood sampled is consistently high and repeat sampling is minimised
(3) A dedicated neonatal laboratory service which allows close liaison with laboratory staff. Collection problems can be discussed easily
(4) Use of manual methods which reduce the volumes required—for example, by predilution. The quality of staff training must be of a high standard to maintain high quality assurance

Therefore even without a major technological advance, progress can be made to reduce the size of blood samples and limit the need for transfusion

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Whole blood assay of theophylline concentrations using immunochromatographic stick

Sir,

Elias-Jones and colleagues have shown that in 77 pairs of samples the mean difference between theophylline concentrations measured by a new method and a standard method was small [1] They have not, however, presented their raw data or the standard deviation (SD) of the mean differences. Provided differences within the range mean difference +2 SD to mean difference −2 SD would not be clinically important the two measurements could be used interchangeably, and so it is important to know that the SD is not unacceptably large Bland and Altman have recently outlined a simple method for assessing agreement between two methods of clinical measurement and have demonstrated how this can be presented [2]

It is also important to know how many comparisons were made at the upper and lower limits of the therapeutic range The clinician not only needs to know how well the new method of assay of theophylline concentrations agrees with the standard method when concentrations are within the therapeutic range but also how well they agree in the potentially toxic and subtherapeutic ranges Does the scatter of differences increase as the values increase, especially when values are >100 mmol/l? This information needs to be available before the new method of assay of theophylline concentrations can be substituted for a standard method

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Hydrops fetalis due to abnormal lymphatics

Sir,

Windebank *et al* reported a case of hydrops fetalis due to abnormal lymphatics [1] The baby, a girl, died at the age of 66 days. We are not aware of any other reports of this condition. Her parents have now had a second female child, with features similar to the first, born 16 months later This baby died age 1 hour We write to report her clinical history.

The parents are members of a travelling family. The mother's previous obstetric history was one pregnancy lasting 42 weeks and delivering a well male infant, weighing 3500 g, a miscarriage at 12 weeks, and the girl reported by Windebank *et al*. In the current pregnancy she first attended the antenatal clinic at 18 weeks, and serial ultrasound scans from 20 weeks showed fetal ascites and massive and increasing oedema She went into spontaneous labour at 32 weeks The membrane rupture delivery interval was 2 hours and 45 minutes, and she was delivered vaginally of a hydropic female infant whose weight was 3010 g, length 41 cm As with the previous pregnancy the placenta was retained, requiring manual removal under general anaesthetic It weighed 725 g and was pale and oedematous

The baby's heart rate was 60/minute, but respirations were absent. She was intubated and ventilated Intensive treatment, including external cardiac massage, failed to improve her condition, and she died at age 1 hour. Blood was obtained from an umbilical venous line. The baby's blood group was A positive, as was her mother's, haemoglobin concentration was 114 g/l and packed cell volume 42·0%, concentration of serum albumin was 18 g/l, serum sodium 130 mmol/l, serum urea 2·3 mmol/l, and serum calcium 2·31 mmol/l.

Postmortem examination showed massive ascites and large serous effusions in both pleural cavities with anatomically normal, but hypoplastic, lungs. Apart from oedema the urinary system appeared normal, as did the heart, the great vessels, the liver, and the spleen. Probably this baby had the same condition as her sister. It is of note that with each baby there was a retained placenta This baby appears to have been the more severely affected.

Windebank *et al*, thought the parents not related.[1] Questioning of the family at the time of the birth of this child, however, established that the baby's paternal grandmother and maternal grandfather are first cousins This was probably overlooked by Windebank *et al*, and this cause of hydrops fetalis may represent a previously unreported autosomal recessive condition Perhaps it should be looked for in travelling families

Reference

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Categories of neonatal care and nurse staffing

Sir,

The English National Board (ENB) for Nursing, Midwifery and Health Visiting recently circulated guidelines for staffing of neonatal units [1] Their document recommends staffing levels in relation to three clinical categories of newborn care over and above normal care—namely, special care, high dependency care, and intensive care The document cites the 1984 British Paediatric Association/British Association for Perinatal Paediatrics (BPA/BAPP) statement[2] on this subject and indeed includes their categories as an appendix. Unfortunately, there has been a major inaccuracy in transcription to which we feel attention must be drawn before further confusion arises The BPA/BAPP document describes eight groups of infants deemed to be in need of intensive care with appropriate nurse staffing The ENB document, on the other hand, restricts intensive care to just the first two of these groups· infants receiving respiratory support and those receiving total parenteral nutrition The remaining six groups are described as belonging to a new category of high dependency care with a reduced level of nurse staffing This is not only likely to cause confusion but is, in our view, ill advised as many of the infants in groups three to eight of the BPA/BAPP document require as much or more nursing attention as those in groups one and two. For example, they include babies with unstable cardiorespiratory disease, babies in the first 24 hours after major surgery, those of less than 30 weeks' gestation during the first two days, babies who are convulsing, those being transported between units, and those undergoing major medical interventions such as peritoneal dialysis or exchange transfusion We very much hope the ENB will reconsider their document and hopefully bring it into line with the paediatric recommendation At least if they do not do so it is important that everyone should be aware of the transcription error that has been made

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Successful suprapubic aspiration of urine

Sir,

O'Callaghan and McDougall recommend the use of ultrasound scanning of the bladder in infants for successful suprapubic aspiration of urine [1] Collection of urine by suprapubic aspiration for accurate diagnosis of urinary tract infections in the newborn infant is not in doubt and is generally accepted

The results of their study show only a 36% success rate of bladder aspirations without the help of ultrasound scanning In the same group they also failed to obtain urine in seven infants despite three repeated attempts There was, however, no mention made as to when these repeated attempts were made

I have been quite successful in collecting urine from infants by suprapubic aspiration by following simple and useful guidelines. I do not attempt suprapubic aspiration until at least 30 minutes after a feed is given

In those babies who need 'full sepsis' screening, urine is collected by suprapubic aspiration at the beginning of the investigation before venepuncture and lumbar puncture I also ask a nurse to keep a sterile container ready to collect urine if the infant voids urine spontaneously during the preparation An appreciable number of infants seem to void urine per urethra just at the time when the skin over the bladder is cleaned! In the rare event of a failed attempt I repeat the procedure one hour later Complications such as bowel perforation and secondary infection after repeated attempts, as mentioned by the authors, have not been experienced by us.

I am surprised at the optimism of O'Callaghan and McDougall for the increasing availability of ultrasound machines in neonatal wards, paediatric wards, and even in the community This may well be true for Melbourne and for teaching hospitals but this has not been my experience in district hospitals

Portable ultrasound machines are still a luxury in many paediatric departments in district hospitals even in the United Kingdom I have difficulties in getting an adequate supply of neonatal incubators or paediatric infusion pumps among many other essential items of basic equipment required for maintaining an effective paediatric service

With continuing cuts in the National Health Service budget it is most unlikely that portable scanners would be available in neonatal or paediatric wards in district hospitals in the distant future In my opinion availability of scanners in the community would remain a dream for some time to come

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Cord blood IgE and month of birth

Sir,

We read with interest the study on cord blood IgE in relation to month of birth by Dr Kimpen and colleagues [1]

Using stringent criteria for detecting maternal fetal blood contamination (IgA >32 3 µg/ml) the authors were able to achieve a low contamination rate of 2·9% compared with the 3 9% that we found in a recent study that we undertook of 153 samples, collecting cord blood by venepuncture and using a higher level of IgA cut off (IgA >100 µg/ml) [2] Was their cord blood sampled by venepuncture or 'squeezed out' from the cut umbilicus? If 'squeezed out' cord serum gives a contamination rate as low as that described, then we should *not* be using a more expensive and time consuming method of sampling by venepuncture as advocated by authorities in this field.[3]

We are also interested in the IgE values of Kimpen's 157 samples showing evidence of 'contamination' indicated by IgA concentrations >3 SD above the mean In our recent study using an IgA >100 µg/ml as cut off, we found six of the 153 samples (3 9%) showing evidence of contamination Among these only three had IgE >1 IU/ml, the remaining three had IgE values of <0·12 IU/ml Thus IgA may not be a truly specific marker for maternal fetal blood contamination.

Finally, we wonder why the incidence of raised IgE in Belgium in 1985 was only 50% of that of Swedish babies in 1979 [4] Might it represent a secular trend of change in allergy predisposition, ethnic or environmental differences, or methodological changes in screening techniques for IgE at extremely low concentrations that has taken place during this period of time.[1 2 4]

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Drs Kimpen, Embrechts, Callaert, and Bosmans comment.

We thank Drs Tseng, Lam, and Davies for their interesting remarks concerning our article in the Archives The difference in contamination rate (2·9% *v* 3·9%) is small and may not be significant when both groups are compared. The number of serum samples examined (5838 *v* 153) may be partially responsible for it

The cord blood samples were taken directly from the umbilical stump immediately after it was cut

Of the 157 cord blood samples with a IgA value higher than 32·3 ug/ml, 79 samples had a IgE concentration higher than 1 IU/ml (50%) In general the absolute IgE concentration tended also to be higher in the group with a high IgA Only 30 samples had a concentration below 0·4 IU/ml (19% *v* 90% in the group with an IgA concentration below 32·3 ug/ml) and 14 samples had an IgE concentration below 0·2 IU/ml (8% *v* 72% in the group with a low IgA concentration) From this study it can be concluded that IgA concentration in the cord blood is a good marker for contamination with maternal blood

We do not have an exclusive answer on the last question Methodological change in screening technique is most probably not responsible for the difference in incidence because the values that would make the difference lie near the cut off point

Figures 1 and 2 of our paper show that the normal values are clustered around the lower limit of the interval between 0·01 and 1 IU/ml We do not think that a difference in detection methods could possibly make such a remarkable difference as 50%. Ethnic and environmental differences cannot be ruled out as causative mechanisms and could indeed be responsible for the lower incidence of raised cord blood IgE in Belgium

Loose hair on toys

Sir,

Loose hair on toys is considered to pose a potential asphyxiation hazard to children There has been a single tragic death where loose fibrous hairs from a toy were present in the child's trachea. However, there is a dearth of evidence of other problems associated with hair or with pile fabric For example, a detailed breakdown of the Department of Trade and Industry's Home Accident Surveillance System 1984 data on accidents concerning toys contains no reports of ingestion or inhalation of hair or fur from pile, and no other deaths have been reported from this cause. Nevertheless, some concern is being expressed in various quarters about this matter

There are many other forms of childhood accident which occur frequently and whose cause is well proven The Child Accident Prevention Trust is concerned that energy and resources are being diverted from these problems into consideration of the possible problems of hair on toys Accordingly, we are asking other medical practitioners to report any experience they have of real difficulties caused by inhalation or ingestion of hair or fur pile, so that we may develop an informed opinion as to whether this is a genuine hazard

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Sex ratio and heterozygote advantage in cystic fibrosis: hypothesis and research proposal

Sir,

Cystic fibrosis is a serious disease probably caused by autosomal recessive transmission. In some white populations it is relatively common, and in such populations the gene frequency has been estimated at around 0·02 Such a value would seem too common to be maintained by mutation, so workers have proposed that some form of heterozygote advantage may be responsible for keeping the gene frequency so high No disease has been identified to which heterozygotes are resistant, but it has been shown that sibships containing affected cases are larger than control sibships.[1] This line of argument is not conclusive, however, because in such studies parents at risk are discovered only if they have an affected child, and the larger the sibship the more likely this is to happen. This objection does not apply so forcibly to those studies showing that grandparents of affected children produced more offspring than grandparents of normal controls.[2] Moreover it has been found that uncles of affected children sire larger sibships than normal controls.[3] Thus it seems that heterozygotes for cystic fibrosis, particularly males, are more fertile than controls Why should this be so? I wish to suggest an answer

There is an excess of male offspring in sibships with cystic fibrosis both among the affected and the unaffected Moreover this male excess extends to the children of the uncles of patients (table), so it seems that men heterozygous for cystic fibrosis sire large families with an excess of male offspring.

I have offered evidence that the sexes of human offspring are partially determined by parental hormone concentrations at the time of conception, high concentrations of testosterone being associated with the subsequent births of sons [4] High androgen concentrations may be assumed to be associated with fertility either through behavioural or physiological mechanisms Accordingly I hypothesise that men heterozygous for cystic fibrosis have high androgen concentrations. If this were true, it might explain, firstly, the high sex ratios in cystic fibrosis sibships

Table *Sexes of cases of cystic fibrosis and their relatives*

Source		*Males*	*Females*	*Males per 100 females*	χ^2	*p Value*
Danks *et al*[2]	Cases of cystic fibrosis	190	155	122·6	1·87	NS
Todd[6]	Cases of cystic fibrosis	37	21	176·2	3·6	NS
Danks *et al*[2] *plus* Todd[6]	All cases of cystic fibrosis	227	176	129·0	3·9	0·05
Danks *et al*[2]	Unaffected siblings of cases	256	200	128 0	4·1	0 05
Pritchard *et al*[3]	Offspring of uncles of cases	41	23	178·3	4·1	0·05
Pritchard *et al*[3]	Offspring of aunts of cases	38	32	118·7	0·2	NS

In order to estimate the significance of the sex ratios in the table, one has to choose an expected value Sex ratios for white people are generally higher than those for black people, 105·8 males per 100 females is reasonable for a white value [5] All the χ^2 values in the table have been calculated on the basis of this expected value The total number of cases and their unaffected siblings and cousins comprise 562 males and 431 females, giving a sex ratio of 130 4 (with $\chi^2=10{\cdot}7$, $p\simeq 0{\cdot}001$, tested against this expected sex ratio)

(both affected and unaffected), secondly, the high sex ratio in the sibships sired by uncles of cases and thirdly, the high relative fertility of male heterozygotes, thus accounting for the high gene frequency

To test the hypothesis, I suggest that the androgen concentrations of men heterozygous for cystic fibrosis should be contrasted with the androgen concentrations of controls

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Archives of Disease in Childhood, 1988, **63,** 576–577

Book reviews

Cystic Fibrosis: the Facts. By Ann Harris and Maurice Super. Pp 133· £8·50 hardback Oxford University Press, 1987. ISBN 0–19–261462–2.

This book is one of a series on medical topics published by Oxford University Press. It s a compact book of modest price intended for the non-medical reader who wishes to know more about cystic fibrosis.

The book attempts to explain the genetics, pathophysiology, bacteriology, and clinical feature in terms comprehensible to the layman This is an ambitious task and non-medical staff who have read it find it heavy going. Because the book concentrates on facts rather than controversies current debates on antibiotic regimes are glossed over and newer ideas on nutrition receive only brief mention The authors' interest in the genetics comes across well in the longest chapters dealing with these exciting developments

This is not an easy book for parents but can be strongly recommended for non-medical members of the cystic fibrosis team.

J J COGSWELL

Children's Health and Well-being in the Nordic Countries. By Lennart Kohler and Gunborg Jakobsson Pp 148: £12·00 hardback Mackeith Press, 1987

The Nordic countries have, for many years, headed the international league table of indices of the health of children—for example, perinatal, infant, and childhood mortality rates and the proportion of infants of low birth weight. This book provides an excellent review, not only of these hard indices but also of the softer indices of morbidity

The introductory chapters set the scene with a wide ranging coverage of relevant information such as demographic change, expenditure on health services and on social services, employment, and the levels of health service provision Wherever possible comparative data for the three monarchies (Denmark, Norway, and Sweden) and the two republics (Finland and Iceland) are given

As expected, most of the routinely collected sources of data are covered They include mortality statistics, cancer and congenital malformation registration, and hospital bed use The last of these has always shown that a hospital bed which is available will be filled I learnt that this has been translated into the third law of thermodynamics—that is, that a hospital bed must be kept warm One surprising omission of what, presumably, is routinely collected, is data on immunisation rates, perhaps because deficiency in immunisation uptake is not a problem of the Nordic countries.

The variety of information provided from special surveys, which range from chronic disability and handicap through drug use in children to interviews and questionnaire data on children's health, is valuable Inevitably, intercountry comparisons are fraught with difficulty because of differences in definition and methods of data collection Among the survey data it is disappointing that there is nothing on breast feeding

The authors carefully define the terms impairment, disability, and handicap but then confine themselves to using only the term handicap when often disability is more appropriate This is a minor criticism, however, as the book in general is a most valuable source of comparative data

P O D PHAROAH

Occupational Therapy for Children with Disabilities. By Dorothy E Penso Pp 181 £8·95 paperback Croom Helm, 1987 ISBN 0-7099-4049-1

This is a volume in the *Therapy in Practice* series edited by Jo Campling The author comments that this book attempts to look deeper and beyond individual impairments to the basic approach of the occupational therapist to the child with disabilities and his family. In this the author has been successful. In general terms the text is somewhat pedantic, but where there are detailed case histories the sequence of history taking, assessment, and case management is clearly set out The need for evaluation is not forgotten It is a pity that in this exciting era of microtechnology the reference to the compensation for motor problems by custom designed switches should have been limited to paragraph in chapter 3.

The illustrations are few and imagination, especially when comp with those of Nancie Finnie's superb b *Handling the Cerebral Palsied Chil Home.*

With the increasing integration children with disabilities and the t towards multidisciplinary training, t caring for children are well informed ready to be partners with the therap

While recommending this book as introduction to occupational therapy children who are disabled, I stro recommend that those who are intere should follow up references in the te gain a comprehensive picture of the we of expertise that is available

R M POV

Haematology of Infancy and Childhood. D G Nathan and F A Oski (2 Vols) ed Pp 1680, £55 hardback Saun Publications, 1987

A review of this tome is a herculean and the true assessment of its worth n await the test of time on our bookshelve the standard reference It might app sacrilegious to criticise the 'bible' of field of work but there are a few comm worth making The weight is consider greater than Gideon's equivalent an could usefully be reduced by omissio the section on disorders of bilirubin m bolism and non-haematological malig cies, which the authors present excelle elsewhere. The colour plates are not reproduced and do not add a lot to book I would have preferred to see a m extensive review of immunophenotypin leukaemia, especially acute myelobla leukaemia where diagnosis—for exam of megakaryoblastic variants—would be helped by the information presente was also very disappointed to see a pe tence of the old canard about fetal hae globin always being raised in Diam Blackfan anaemia In an otherwise ex lent section the true heterogeneity of disorder and difficulty in distinction f transient erythroid aplasia is again glo over.

The new edition is outstanding value for oney being much cheaper than smaller id less useful texts. The reference lists are markably up to date and I thoroughly njoyed the new information on molecular ology In addition there were very few pographical errors and the layout of the ook is very good. No paediatric haemato- gy department will be complete without and it remains the standard text for hae- atologists and others who manage child- n with blood disease

I M HANN

ıtimicrobial Therapy in Infants and hildren. Edited by Gideon Koren, harles G Prober, and Ronald Gold Pp 9 hardback (price not stated). Marcel ekker, 1988 ISBN 0-8247-7745-X

his is volume 4 of '*Clinical Pediatrics*', a ries edited by Fima Lifshitz of Cornell niversity and designed to provide '. an cellent data base for physicians . . . to d them in their clinical practice . ' he remit to provide a data base has ertainly been fulfilled The book is an cyclopaedic resource for almost every- ung known about antimicrobial drugs, id it provides authoritative well refer- nced guidelines for their use, drug by rug, in infancy and childhood

Where I feel that the book fails seriously . in its second declared aim The layout of ie book is by drug: chapter 17, macrolide ntibiotics; chapter 18, the lincosamides, ather than by condition—for example, ieningitis—and it is not at all easy to xtract disease oriented information This lentifies the major failing in my eyes, the idex, which is frankly inadequate to deal rith clinical issues For example, to re- rieve information on the use of antimicro- ial prophylaxis in the family of a child rith meningitis caused by *Haemophilus ıfluenzae*, you might look up the organism in the index: all you find is an arcane reference to the antimicrobial activities of pefloxacin, amifloxacin, enoxacin, and norfloxacin. Still game, you look up meningitis. the single reference now is to a table suggesting the empirical selection of ampicillin and tobramycin as first choice therapy for neonatal meningitis, and ampicillin and chloramphenicol for older children Prophylaxis—a bit desperate, this—raises no reference at all If you already knew that rifampicin was the drug to consider, then in the rifampicin chapter you would find the information—a short, referenced section on the prophylaxis of *H influenzae* contacts, cross referenced to elsewhere in the text for dosage recommendations

My colleagues in the hospital pharmacy like this book for its compendious nature and its emphasis on pharmacokinetics and pharmacodynamics. They'll get my copy, and perhaps hospital pharmacies in general might consider buying it, but I cannot recommend it for the practising paediatrician.

J S KROLL

Oncology and Immunology of Down Syndrome. Edited by Ernest E McCoy and Charles J Epstein Pp 242. hardback (price not stated) Alan R Liss, 1987. ISBN 0-8451-5096-0

People with Down's syndrome have an increased risk of infection, particularly respiratory infection, and an increased risk of developing acute leukaemia Scientists are only just beginning to realise the potential of children and adults with trisomy 21 to teach us about resistance to infection and aspects of oncology. The Epsteins, Lois and Charles, have been at the forefront of recent advances, showing by studies on trisomic fibroblasts that the genes coding for the receptors for interferons α and β are on chromosome 21 Furthermore an oncogene has recently been localised to 21q22, raising important but unanswered questions about oncogenesis

This book constitutes the proceedings of the annual United States National Down Syndrome Society symposium held in December 1986. As such it suffers from the usual problems of published proceedings with papers in different typesettings of variable quality, considerable overlap of content, and variable quality of papers. There is an excellent short introduction on the molecular biology of chromosome 21 The rest of the book is divided into separate sections on oncology and immunology. It is evident from both sections that there are too few scientists working in either field to fill a book. The oncology section veers off into a chapter on chromosomal translocations in B cell derived tumours of only peripheral relevance to Down's syndrome, and another chapter on lineage establishment in haemopoiesis that was interesting but obscure In the immunology section the emphasis drifts from specific immune defects in subjects with Down's syndrome to more recherché aspects of interferon On the credit side there is a fine chapter by the Epsteins and Jon Weil describing the mouse model trisomy 16

This book is an indictment of how we have neglected children with Down's syndrome, know far too little about the epidemiology or aetiology of their infections, and have thus been slow to learn important lessons from this 'experiment of nature ' I suspect it will have a very limited readership and I would certainly not recommend it as a book to be purchased for clinics dealing in practical aspects of managing children with Down's syndrome I hope though that those interested in basic science will read and take note

D ISAACS

Archives of Disease in Childhood, 1988, **63,** 578

British Paediatric Association

A gem of a book

Child Health in a Changing Society. Edited by J O Forfar. Oxford University Press, 1988.

The British Paediatric Association, founded in 1928, has put together as part of its Diamond Jubilee celebrations a really sparkling book. Designed to be read by interested lay persons as well as by health professionals, it fully deserves the prestigious imprimatur of the Oxford University Press.

The secret behind the sparkle is the inspired choice of authors—one, two, or three for each of the nine chapters—and the sure editorial touch of the Association's President, John Forfar. Each chapter reviews the events of the past 60 or so years in the relevant field, describes in non-specialist terms the present state of the art, and—with varying degrees of diffidence—hazards some predictions for the future. All the authors recognise explicitly the reciprocal relationship between health professionals and the rest of society. They and their colleagues exist to serve the children in their communities, from conception to adulthood, but their activities are greatly influenced by the expectations of those communities, their behaviour, their ethos and (coming down to earth) the resources which they allocate to the child health service.

Donald Court (a distinguished Past President of the Association and architect of the Court Report on Child Health Services) joins forces with Eva Alberman to review progress in child health since the turn of the century, and to take a critical look at the state of affairs today. There is cause for gratitude but not for complacency.

David Baum and Martin Bobrow discuss the prospects for preventing congenital and genetic disease explaining a highly technical field in commendably non-technical terms. Clearly we shall soon have new powers that we must learn to use wisely.

Richard Cooke and Pamela Davies review progress in the care of the newborn, and bravely address some current dilemmas concerning sickly babies and scarce resources. As in genetics, we must distinguish between what is possible and what is proper.

Martin Bax, Roger Robinson, and Ann Gath write about 'The Reality of Handicap' with a great breadth of knowledge and understanding. Science and compassion go hand in hand. Jean Golding, David Hull, and Michael Rutter take an equally broad brush approach to the influence of environmental factors on child health, and manage to keep all six feet on the ground when discussing such emotional topics as air pollution, zinc deficiency, and food additives.

Aidan Macfarlane and Ross Mitchell look at the links between health, social and educational services, and the importance of those links to child health and development. They see much yet to be done. and little but indifference to delay it.

By this point, gentle reader, you may have noticed that we have not yet set foot in the children's ward (except the neonatal unit). Roy Meadow's evocative and perceptive chapter starts with the unacceptable face of hospital paediatrics 60 years ago and ends with a lament for the second class citizenry of children in District General Hospitals, but there is much cause for rejoicing in between. Alex Campbell tackles with clarity and authority the ethical problems that beset paediatric practice and research, and which seem likely to perplex us even more in the future. Finally, John Forfar contributes a masterly overview of how paediatrics itself has changed since the BPA began.

Nine chapters there may be, but this is not a book of parts. It stands as a whole, enormously informative, totally readable, thoroughly enjoyable. Unlike most medical textbooks, it will remain informative and enjoyably readable for years to come. Parents, teachers, and social workers, as well as doctors and nurses, will find pearls within this diamond. And the breadth of the canvas so colourfully covered serves to remind us all how fortunate we are to be serving Child Health.

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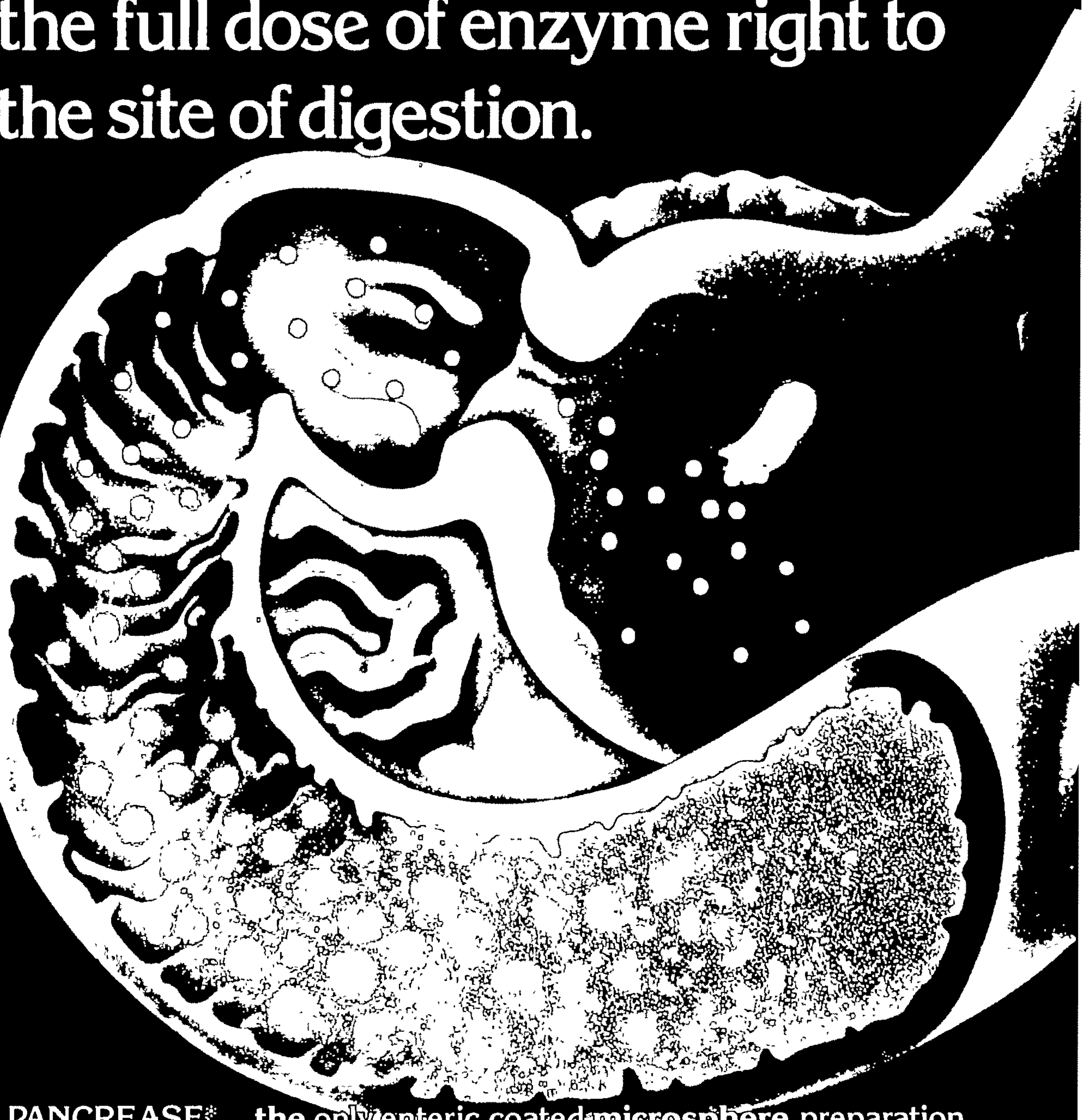

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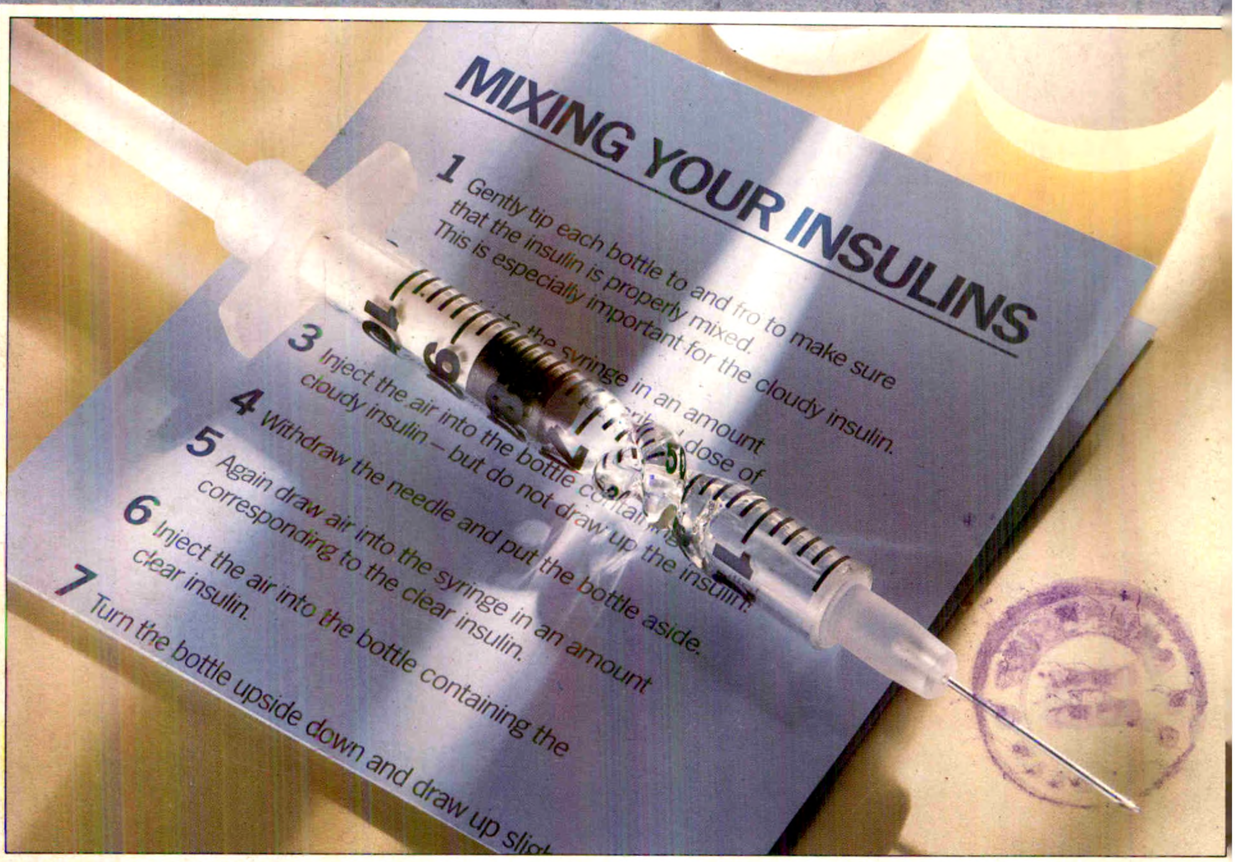

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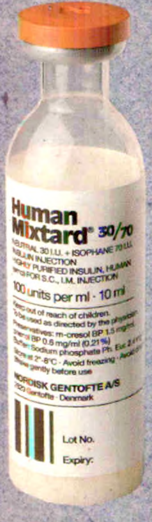

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Archives of Disease in Childhood, 1988, **63,** 1119–1121

Annotations

The fetus of the diabetic mother: growth and malformations

Since Pedersen[1] put forward the hyperglycaemia hyperinsulinaemia hypothesis as an explanation of the aetiology of diabetic fetal anomalies the care of the pregnant diabetic patient and her fetus has greatly improved. If the diabetes of the mother has been well controlled during pregnancy, the newborn child is not grossly overweight, the perinatal morbidity is low, and hypoglycaemia and other neonatal complications can be successfully treated. Despite these improvements, however, there has been no change in the incidence of malformations in these neonates, and this remains the greatest problem in the management of the pregnant diabetic woman.[2]

In studies of the effects of diabetes on the fetus and malformations, experimental animals have been widely used. Many rodent models of diabetic pregnancy have, however, several shortcomings. These include: retardation of fetal growth and reduction rather than increase of birthweight,[3–5] hyperinsulinaemia does not occur[4] and the islets of Langerhans are hypotrophic rather than hypertrophic.[6] In one specific Sprague-Dawley rat substrain, however, diabetes during pregnancy causes not only retardation of fetal growth but also a high incidence of skeletal malformations not seen in normal pregnancy.[7] Insulin treatment of the diabetic rats almost abolishes retardation of growth and malformations, but withdrawal of insulin during short specific periods early in pregnancy is enough to induce malformations.[8] Several parallels with human diabetic pregnancy are evident: firstly there is retardation of growth in early human diabetic pregnancy,[9] which is associated with an increased incidence of malformtions in the neonate.[10] Moreover, poor metabolic control early in pregnancy during the sensitive period of organogenesis is also associated with an increased risk of malformations in human pregnancy.[11]

It seems therefore that a suitable experimental model for the study of teratogenesis during diabetic pregnancy is available. In this substrain of Sprague-Dawley rats that is prone to fetal malformations, there is the interaction between genetic factors and the metabolic derangement of diabetes that is necessary for the induction of skeletal malformations,[12] but the nature of the genetic predisposition is not yet clear. It is, however, noteworthy that diabetes exacerbates changes in proteoglycan metabolism in cartilage that are more severe in this substrain than in other Sprague-Dawley strains.[13] Whether malformations in human diabetic pregnancy are linked to genetic markers in the mother or fetus, or both, is open to question.

To explore further how diabetes retards fetal growth and causes malformations, a model system more controllable than an intact animal would be helpful. Tissue culture of whole rat or mouse embryos seems promising in this respect, because the effect of a single substance or metabolite can be measured.[14] Such studies have shown that high plasma glucose concentrations and ketone bodies, alone or in combination, induce retardation of growth and malformations in vitro, in both strains of rats that are prone to malformation and those that are not.[12 15] Plasma glucose concentrations in the hypoglycaemic range have also been shown to induce malformations in vitro.[16] These and other observations have led to the hypothesis that disturbances of the glycolytic flux at a critical developmental stage (and in the absence of other major alternative pathways of metabolism) cause malformations.[15 17] Abnormal glucose metabolism, however, may not explain all malformations,[18] and it does seem plausible that disturbances in the supply of other nutrients such as amino acids and lipids would effect growth and morphogenesis by altering the availability of building blocks for proteins and membranes, or by effects on energy metabolism, or both.[19]

The close association between retardation of growth and teratogenesis has focused attention on the regulation of growth of embryonal cells. In a preliminary study of chondrocyte differentiation of cells in vitro from the particular substrain of rat that is prone to malformations, an inhibition of chondrocyte replication was noted in the presence of ketone bodies or high glucose concentrations. Moreover, chondrocytes obtained from locations at which skeletal malformations have been observed to occur in vivo were more sensitive to the inhibitory effect of glucose.[20] This approach appears promising for the future study of diabetic teratogenesis, and the culture method may provide a screen for putative teratogens.

Many investigations of the regulation of embryonal and fetal growth have not directly addressed the question of teratogenesis but rather studied basal requirements for cellular growth and replication. It seems that prenatal growth is dependent on a complex interaction between the supply of nutrients, circulating hormones, and polypeptide growth factors that act locally.[21] Of the circulating hormones, human placental lactogen has attracted most attention. Synthesised and secreted by the placenta and present in high concentrations in the maternal circulation, it can also be found in appreciable concentrations in fetal blood.[21] Human placental lactogen stimulates replication of human fetal cells in vitro, and this effect is partly mediated by somatomedins and insulin like growth factors.[22] The insulin like growth factors are produced by a number of fetal tissues and are thought to act locally, at or near their site of production.[23] To achieve the optimal effects from the circulating and local growth factors an adequate intracellular supply of nutrients is necessary. Uptake and metabolism of nutrients in the cells is stimulated by insulin, and it has been suggested that this hormone interacts with low molecular weight nutrients to provide an anabolic enviroment that encourages growth.[24] The complicated network of interactions also includes stimulation of insulin secretion in the fetus by nutrients and human placental lactogen and stimulation of human placental lactogen production by insulin.[25–27] The experimental findings are paralleled by the recent clinical observation that maternal human placental lactogen concentrations correlate with the size of the baby at birth and hence, by inference, with fetal growth.[28] It is possible, but not yet proved, that a high production of human placental lactogen is also reflected in the fetal circulation. Moreover, birth weight also varies with differences within the normal range of glucose tolerance.[28 29] Mothers with slow, although not diabetic, disposal of glucose and who thus have wider ranges of blood glucose concentration, transfer more glucose (and perhaps also more of other nutrients) to the fetus, which at birth is larger but of normal adiposity.[28] To benefit from such a rich supply of nutrients the fetus would need a parallel increase in its own insulin secretion. This may indeed be the case because the human fetal B cell is more sensitive to glucose in earlier developmental stages than has hitherto been generally accepted.[27]

Most investigations of the regulation of growth in vitro have been performed with cells taken from human fetuses early in the second trimester, and it is uncertain whether the regulatory mechanisms are relevant for the early embryo. In rodents, however, insulin like growth factors, insulin, and their respective receptors are present early in development,[30 31] and some evidence that they have a role in regulation of growth has been presented.[32] By combining the considerable knowledge on the actions of hormones and growth factors with that on experimental models of teratogenesis outlined above, new insights into embryonal growth and teratogenesis would be gained.[33] Meanwhile, excellent control of blood glucose concentrations before conception is still the best advice for the diabetic woman contemplating pregnancy.

This work was supported by the Swedish Diabetes Association, the Juvenile Diabetes Foundation (grant 185544) and the Swedish Medical Research Council (grants 12X-109 and 12X-7475).

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Archives of Disease in Childhood, 1988, **63**, 1122–1125

Neonatal tumours

Neoplasms discovered at birth or during the first month of life are rare. Less than half are malignant but these represent a range of disease different from that seen in older children with cancer. Furthermore, some tumours which look malignant histologically may show benign behaviour while apparently benign tumours may be fatal by virtue of their position (for example, in the neck, mediastinum, or brain).

Incidence and aetiology

Estimates of incidence are imprecise. There have been few attempts at a population based assessment, most reports representing the experience of single institutions where selection bias reflects referral patterns. Some lesions raise difficulties of distinction between classification as tumours or as congenital abnormalities and most series exclude lymphangiomas, cutaneous haemangiomas, and uncomplicated melanocytic naevi. In the Third National (US) Cancer Survey (TNCS), Bader and Miller estimated the prevalence of malignancy in the first month of life to be 36·5 per million live births, or about 1:27 000,[1] while a report from the British Paediatric Pathology Society estimated the prevalence of congenital neoplasia (benign and malignant) between 1:12 500 and 1:17 300 total births.[2] Perinatal tumours accounted for only 2·6% of all neoplasms recorded in a 25 year period at the Children's Hospital of Los Angeles; 40% were malignant.[3] This figure is somewhat lower than that from the Hospital for Sick Children, Toronto, where malignancies in the neonatal period accounted for 1·9% of all cases of cancer seen over 60 years.[4]

The aetiology of congenital tumours is unclear but an association with other congenital abnormalities is well recognised.[5] In some cases intrauterine environmental factors may be important,[6] and even transplacental spread of maternal tumour has been reported.[7] There is a need for a detailed, population based study to explore the patterns of neonatal neoplasia and associated malformations more fully and to learn more of their natural history and treatment prospects. Such a study is being prepared by the United Kingdom Children's Cancer Study Group (UKCCSG).

Teratomas

These are the most frequent perinatal neoplasms, accounting for between a quarter and one third of cases.[2 3] They are very rarely malignant—indeed they did not appear at all in the TNCS report. The sacrococcygeal region is the most common site.[3 8] It is of interest that although two thirds of all sacrococcygeal teratomas are reported in the neonatal period, the risk of malignancy is small but increases substantially in those diagnosed later in infancy.[9] Typically sacrococcygeal teratoma (which occurs predominantly in girls) presents as a large cystic but well encapsulated mass extruding from the coccyx, although part or all of the tumour may be presacral. Solid tumours should be viewed with greater suspicion as they are more likely to contain malignant elements.[3] Total excision of the tumour is mandatory as histologically benign residual tissue may recur as malignant tumour.[9]

Soft tissue tumours

Benign and malignant soft tissue tumours are relatively common and, grouped together, exceed both neuroblastoma and leukaemia, the two most common malignant diagnoses.[3] Tumours of fibrous tissue predominate and account for perhaps two thirds of soft tissue neoplasms in neonates,[3 10] consisting mainly of the fibromatoses (infantile fibromatosis and myofibromatosis) and fibrosarcoma. They occur particularly in the head, neck, and extremities and are locally aggressive to varying degrees. Although the histological appearance of congenital fibrosarcoma is no different from that observed in the older child or adult, it seldom metastasises and has a good prognosis, although radical surgery may be required to achieve local control.[11] Rhabdomyosarcoma, the commonest soft tissue malignancy in older children, is very rare in the neonatal period, although presentation, prognosis, and treatment are similar.[10] Haemangiopericytoma, undifferentiated sarcoma, and leiomyosarcoma have also all been reported in neonates.[3 4]

Neuroblastoma

Neuroblastoma is the most common type of malignant tumour, accounting for 30–50% of cases in most series.[3 4 12] An abdominal mass is the commonest presentation either from the primary tumour or liver metastases, while unilateral Horner's syndrome (in cervicothoracic primaries) and spinal compression (in paravertebral tumours) are alternative signs of disease. Most neonates with disseminated neuroblastoma have stage IVS disease (a localised primary with metastatic disease confined to liver, skin, and bone marrow).[13] Their prognosis is good, many showing evidence of spontaneous disease regression. The mode of treatment can be controversial but should be restricted to the minimum necessary to prevent life threatening complications.[14] The unusually good prognosis of neuroblastoma in very young children is not restricted to those with IVS disease and patients with stage II (postoperative microscopic residual) also benefit from a conservative approach. The unusual biology of neuroblastoma is shown by the description of neuroblastoma in situ, which consists of nests of neuroblastoma tissue in an otherwise normal adrenal medulla, unassociated with gross tumour or metastases. This has been reported in 1:200–1:500 fetal and infant postmortem examinations.[15] The significance is uncertain but is widely believed to represent a potentially malignant neoplasm which can regress spontaneously. Interestingly, there appears to be a high incidence of associated congenital abnormalities in this condition.[3 15]

Leukaemia

Leukaemia occurs with a frequency somewhat less than neuroblastoma but significantly in excess of other malignant solid tumours. Unlike the disease in older children, acute non-lymphoblastic leukaemia predominates. The diagnosis is not always straightforward and it is important to consider the possibility of haemolytic disease, congenital infection, or disseminated neuroblastoma among the differential diagnoses.[16] There is a well known association with children with Down's syndrome, in whom transient congenital leukaemoid reactions are also seen,[17] although these have also been reported in phenotypically normal newborns.[18] Skin nodules from leukaemic infiltrations are not infrequent and are often associated with monocytic subtypes, for whom an improved prognosis has been suggested.[19] Overall, however, the prognosis is poor and leukaemia accounts for more deaths than any other type of neonatal malignancy.[3 4]

Brain tumours

About 1% of childhood brain tumours occur in the neonatal period, an incidence much lower than in later childhood.[1 3] The commonest presenting features are hydrocephalus, which may be severe enough to cause cephalopelvic disproportion during labour, and vomiting. Differences from the pattern of disease seen in older children include a high incidence of teratoma and a predominance of tumours in supratentorial sites.[20] Many neonatal brain tumours are very large at diagnosis and have a high incidence of spontaneous haemorrhage into the tumour mass, factors which contribute to their poor prognosis.[20]

Renal tumours

These are uncommon in the neonate, although renal masses are not; hydronephrosis and cystic kidneys being the most important non-neoplastic causes. Wilms' tumour occurs but is exceptionally rare and in the past was often confused with mesoblastic nephroma (fetal renal hamartoma).[21 22] This is generally considered to be a benign condition cured by surgery alone, although local recurrence can occur and one case of metastasis has been reported.[23] True Wilms' tumour occurs much less frequently,[24] and both favourable and unfavourable histological variants have been reported. Neonatal diagnosis does not appear to be an adverse prognostic factor. The finding of nephroblastomatosis (nodular renal blastema) in 1:300–1:400 necropsies draws analogies with neuroblastoma in situ, and its role as a precursor of Wilms' tumour has been discussed.[25] It is reported in particularly high frequency in children with bilateral tumours.

Liver tumours

Liver masses in the neonatal period are most likely to be non-malignant, haemangioma and mesenchymal hamartoma being the most frequent diagnoses, although their true incidence is unknown as they are sometimes incidental findings at necropsy. The incidence of metastatic neuroblastoma or leukaemia exceeds the frequency of primary malignant liver tumour[3] and although 60% of hepatoblastomas occur in the first year of life, diagnosis in the neonatal period is uncommon.[26] Typically, liver tumours present as an abdominal mass that may cause respiratory embarrassment. Haemangioma may be associated with anaemia, progressive cardiac failure, and comsumptive coagulopathy, and the presence of cutaneous haemangiomas may provide an additional clue.

Retinoblastoma

The presentation of retinoblastoma in the neonatal period will be influenced by the policy of elective examination of the eyes of children with a family history of the disease. This accounted for almost 25% of children with retinoblastoma in the Toronto series,[4] which showed an unusually high incidence of neonatal diagnosis (11·5% of all cases known to the hospital). Most had bilateral tumours consistent with the inherited form of the disease.

Histiocytic syndromes

Langerhans cell histiocytosis (histiocytosis X) is no longer considered to be a neoplastic process[27] and its presentation in the neonatal period is distinctly uncommon.[3] Haemophagocytic lymphohistiocytosis, although very rare, is usually familial and may present very early in infancy.[28]

Management

Neonatal tumours present particular difficulties, although the broad principles of managing malignant disease are the same as in older children. The special behaviour of neonatal neuroblastoma and the relatively benign nature of infantile fibrosarcoma provide examples of a need for a conservative approach. Surgery plays the major part in the management of benign, and many malignant, tumours. The role of chemotherapy and especially radiation must be carefully considered on an individual basis. Drug doses should be calculated according to body weight rather than surface area and started at reduced levels, increasing as tolerated.[29] The use of radiation treatment is of concern in view of the extreme immaturity of normal tissues and the potential for late effects on growth and the risk of second malignancy.[30] There is increasing interest in the use of chemotherapy rather than radiation for the treatment of infants with brain tumours[31] and in the need to replace or defer radiation as prophylactic treatment of the central nervous system in infants with leukaemia.[32]

Neoplasia in the neonate is uncommon and the pattern of disease so unusual that treatment must be 'tailored' for each baby. Nevertheless, a large number of children can be successfully treated although most, including many with apparently benign disease, would benefit from the diagnostic and therapeutic resources of a paediatric oncology centre.

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Archives of Disease in Childhood, 1988, **63,** 1126–1130

Transient hyperoxia and cerebral blood flow velocity in infants born prematurely and at full term

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SUMMARY Little is known about the effects of hyperoxia on the cerebral circulation of human infants. Using duplex Doppler we measured the changes in cerebral blood flow velocity in a group of full term (n=15) and premature infants (n=17, median gestational age 31 weeks) in response to a transient threefold increase in oxygen tension. Measurements of blood gas tensions as well as blood pressure and cerebral blood flow velocity were made over a period of 20 minutes on three occasions for each infant; during normal oxygenation, hyperoxia, and normal oxygenation. There was a fall in cerebral blood flow velocity in 15 of the 17 premature infants with hyperoxia and the median reduction was 0·06 cm/second for every 1 kPa increase in oxygen tension. There was no significant change in either PCO_2 or blood pressure during the period of hyperoxia. The cerebral blood flow velocity fell in all 15 infants born at full term during hyperoxia, but there was a simultaneous and significant reduction in PCO_2 at the same time as the hyperoxia. Analysis of variance suggested that in the infants born at full term the change in carbon dioxide had most effect in the reduction of cerebral blood flow velocity, rather than the hyperoxia itself. We conclude that in premature infants, cerebral vascular resistance may be altered by a fall in cerebral blood flow velocity in the presence of hyperoxia.

Hyperoxia has a consistent and predictable effect on cerebral blood flow in healthy adult brains. Little is known, however, about the effect of hyperoxia on cerebral blood flow in newborn infants, although oxygen is commonly used to treat lung disease in this population. Periods of prolonged hyperoxia cause vasoconstriction of the neonatal retinal circulation (which arises from the internal carotid artery) and so would also be expected to have a similar effect on the cerebral circulation. Whether the central nervous system of the extremely premature newborn infant is also sensitive to the effects of hyperoxia is unknown.

We report the use of duplex Doppler ultrasound to study the physiological effect of extremely short periods of hyperoxia on the cerebral circulation in healthy and ill infants born prematurely and at full term.

Methods

Infants enrolled in this study were all born in the maternity unit of the Leicester Royal Infirmary and were selected if they had a normal cerebral ultrasound examination, no serious congenital abnormalities, and no clinical evidence of intrapartum asphyxia. Infants on mechanical ventilators were recovering from their lung disease, and arterial blood gas sampling was performed only through indwelling aortic or radial cannulas.

The infant's gestational age was calculated from the date of the mother's last menstrual period, and if there was any doubt about it a Dubowitz assessment of gestation was performed.[1] There were three groups of infants: those receiving mechanical ventilation with extra oxygen, those requiring oxygen by headbox, and healthy mature infants born at full term with no lung disease.

Measurement of cerebral blood flow velocity was made with an ATL duplex Doppler mark 600 machine. The transducer (724A) contained a 7·5 MHz pulse/echo imaging crystal and a 5 MHz pulse/echo Doppler crystal. At least 20 consecutive cardiac impulses were recorded onto audiotape and subsequently analysed using the computer system described by Schlindwein *et al.*[2] This system performs fast Fourier transform on the audio signal to produce Doppler power spectra every 6·25 ms. A maximum frequency envelope is then extracted from the spectral data using a threshold technique.[3]

The frequency measurements are converted to velocity measurements with the standard Doppler equation, and the mean velocity over the cardiac cycle is calculated by halving the mean measurement of the maximum velocity over the cardiac cycle.[4]

Before the study a transcutaneous oxygen or combined carbon dioxide and oxygen monitor was calibrated and applied to the anterior abdominal wall of the infant. Mean arterial blood pressure was measured by a Dinamap blood pressure monitor or directly from an arterial line where one was available. Each baby was studied under three conditions consecutively: normal oxygenation, hyperoxia, and normal oxygenation. After the transcutaneous monitor had stabilised, a measurement of cerebral blood flow velocity was made from the ascending portion of the anterior cerebral artery as previously described.[5] The amount of oxygen inspired was then increased to produce a measured arterial oxygen tension of about three times the resting measurement. The infant was allowed to stabilise for five minutes and then further recordings of cerebral blood flow velocity, transcutaneous PO_2, mean arterial blood pressure, and $PaCO_2$ or transcutaneous PCO_2 where appropriate, were made. The period of hyperoxia never exceeded 10 minutes. The third assessment of cerebral blood flow velocity, blood pressure, and blood gases was made five to 10 minutes after the concentration of inspired oxygen had been returned to the baseline measurement.

Statistical analyses were by the Wilcoxon paired test, the two tailed Mann-Whitney test, and analysis of variance.

The study was approved by the Leicestershire district ethical committee and infants were enrolled only with the full consent of their parents; the study was usually performed in the presence of the baby's mother.

Results

A total of 32 infants was studied, 17 were premature (36 weeks' gestation or less) and 15 born at full term (37–42 weeks' gestation). The median gestational age of the infants born at full term was 39 weeks and that of the premature group 31 (range 25–36). The median age at the time of the study was 2 days in the premature group and 3 days in the group born at full term (tables 1 and 2).

There were significant falls in cerebral blood flow velocity in 15 of the 17 premature infants with hyperoxia (p=0·001) (fig 1) and in all 15 of those born at full term (p=0·0006) (fig 2). The change in velocity was corrected for a standard rise of 1 kPa in PaO_2. The median reduction in cerebral blood flow velocity for every increase in oxygen tension of 1 kPa was 0·06 cm/second for premature infants and 0·18 cm/second for those born at full term; this difference was significant (p=0·0001).

The median changes in velocity for the normoxic, hyperoxic, and normoxic periods of the study for the two groups are shown in fig 3. There was no difference between the two normoxic periods for the infants born at full term, but in the group of premature infants the velocity remained significantly lower in the second normoxic period compared with the first (p=0·016). The median time between the second and third assessments in the premature group was 10 minutes.

Table 1 *Details of 17 premature babies with hyperoxia*

Case No	*Gestational age (weeks)*	*Birth weight (g)*	*Age at study (hours)*	*Intermittent positive pressure ventilation used*
1	33	1300	6	No
2	25	820	72	Yes
3	32	1930	48	No
4	29	1270	13	Yes
5	29	1430	192	Yes
6	29	1660	35	Yes
7	36	2550	16	Yes
8	34	2220	6·5	Yes
9	33	2320	168	Yes
10	35	1920	48	Yes
11	31	1540	48	No
12	34	1860	48	No
13	34	1890	48	No
14	26	1030	96	No
15	32	2070	15	Yes
16	30	740	30	No
17	32	1390	96	Yes

Table 2 *Details of 15 full term infants with hyperoxia*

Case No	*Gestational age (weeks)*	*Birth weight (g)*	*Age at study (hours)*	*Intermittent positive pressure ventilation used*
1	40	3370	120	No
2	41	3560	48	No
3	37	2190	24	No
4	39	3130	48	Yes
5	38	3800	29	Yes
6	42	3390	18	Yes
7	40	3050	120	No
8	39	2940	96	No
9	37	3090	20	Yes
10	40	3150	240	No
11	39	4140	37	No
12	37	3470	196	No
13	39	3720	72	No
14	38	3430	96	No
15	39	2720	9	Yes

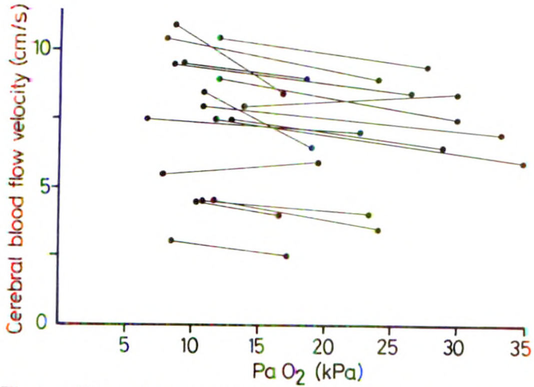

Fig 1 *Change in cerebral blood flow velocity induced by increasing oxygen tension in infants of less than 37 weeks' gestation (p=0·0012).*

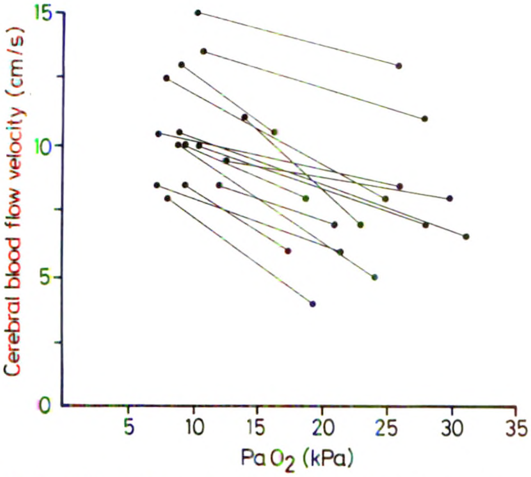

Fig 2 *Change in cerebral blood flow velocity induced by increasing oxygen tension in infants of 37–42 weeks' gestation (p=0·006).*

There were no significant changes in the mean arterial blood pressure during the three assessment periods for either group. In the premature group carbon dioxide tension measurements were available in 13 of the 17 infants and there were no significant differences among the three assessment periods. Carbon dioxide tension measurements were available in 11 of the 15 infants born at full term, and in this group the median carbon dioxide tension for the normoxic, hyperoxic, and normoxic groups were 5·1, 4·7, and 5·0 kPa. When the two periods of normal oxygenation were compared with the hyperoxic period, there was a significant reduction in carbon dioxide tension with rising oxygen (the first normal period compared with the hyperoxic period p=0·007, and the hyperoxic period

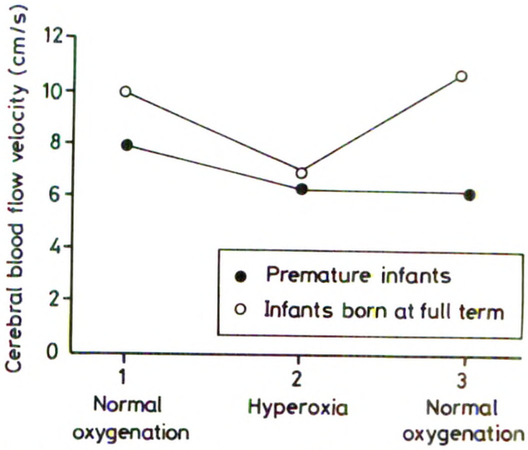

Fig 3 *Median changes in cerebral blood flow velocity at the three assessments.*

compared with the second normal period p=0·05). Analysis of variance showed that a change in oxygen tension contributed 1·3% of the variability in cerebral blood flow velocity compared with 10·6% that was attributable to changes induced by alterations in the carbon dioxide tension.

Discussion

Our study shows that newborn infants undergo physiological changes in their cerebral blood flow velocity with hyperoxia, and this effect was present during the first few days of life. We previously reported that extremely ill, premature infants undergo an increase in their cerebral blood flow velocity with a small increase in arterial carbon dioxide tension.[6] These studies show that in newborn infants irrespective of gestational age changes can be mediated in cerebral blood flow by altering blood gas tensions in the same manner as in adults.

Hypoxia increases cerebral blood flow in fetal[7] and newborn[8] lambs. Rosenberg *et al*[8] also showed that the increase in cerebral blood flow (measured by microspheres and induced by hypoxia) correlated closely with changes in both diastolic velocity and peak systolic velocities (measured by Doppler ultrasound). Costeloe *et al*[9] showed a reduction in apparent cerebral blood flow with hyperoxia using indirect methods of measuring cerebral blood flow such as venous occlusion plethysmography and electrical impedance, but the infants that they studied were more mature than the ones we report.

There has been some suggestion[10] (based on the work of Mchedlishvili[11]) that Doppler ultrasound may not reliably reflect changes in cerebral blood flow caused by the changing diameter of the vessel being examined (in this case the anterior cerebral artery). If, however, hyperoxia did induce vasoconstriction of the anterior cerebral artery, this effect would only underestimate any change detected by Doppler ultrasound. Mchedlishvili recently concluded that changes in cerebral blood flow caused by changes in oxygen or carbon dioxide tensions are mainly mediated through the small pial arteries.[12] We believe that changes in cerebral blood flow velocity measured by duplex Doppler ultrasound reflect actual changes in cerebral blood flow caused by the resistance of the cerebral microvasculature.

The infants born at full term seemed to have greater reduction in cerebral blood flow velocity than the premature ones. This effect was principally caused by significant falls in carbon dioxide tensions during the periods of hyperoxia. Increasing inspired oxygen to the mature spontaneously breathing newborn infant probably stimulated respiration with a consequent reduction in carbon dioxide tension. This may have been mediated peripherally by the flow of gas close to the babies' faces. An alternative hypothesis is that the reduction in pulmonary vascular resistance increased the pulmonary blood flow and hence reduced the $PaCO_2$. We cannot be sure whether hyperoxia alone changes the cerebral blood flow velocity in the mature babies we studied, because of the comparatively greater effect of the change in carbon dioxide tension. Most of the premature infants we studied were mechanically ventilated and consequently did not show systematic changes in their carbon dioxide tensions. Hypoxia and hypercapnia have additive effects in increasing cerebral blood flow[13 14] and we might assume that hyperoxia and hypocapnia have similar additive effects.

Another interesting difference between premature infants and those born at full term was the failure of the premature infants' cerebral blood flow velocity to return to normal after periods of hyperoxia (fig 3). This may be because premature infants have less efficient control of their cerebral arterioles, and there is a delay in vasodilatation and return to normally oxygenated cerebral blood flow. We may also be observing a hysteresis loop with proportionately less reduction in cerebral blood flow velocity in the downward part of the oxygen tension curve. With the introduction of more continuous methods for measuring cerebral blood flow velocity we may be able to study this in more detail.

Infants born at full term (and possibly also premature infants) with sustained degrees of hyperoxia are more likely to develop retinopathy of prematurity and this is presumably due to a period of retinal ischaemia. The retinal arterioles are not likely to be any more sensitive to hyperoxia than other arterioles within the central nervous system, and our results show that there is a consistent reduction in cerebral blood flow velocity (and therefore cerebral blood flow) with a short period of hyperoxia in the immature brain itself. It seems possible therefore, that the effects of a short period of hyperoxia on the brain of an extremely premature infant may be more prolonged than on the brain of a baby born at full term, and that this may be an important factor in the development of retinopathy of prematurity in these infants. We believed that it was justified and safe to expose these infants (most of whom were receiving oxygen anyway) to an extremely short period of hyperoxia. Regular ophthalmic examinations of the premature infants were performed and in no case where acute retinopathy of prematurity occurred was it more severe than grade II.

In conclusion, the cerebral blood flow velocity of the newborn infant alters in response to a brief period of hyperoxia. In the premature infant this effect seems to be more prolonged than that in the infant born at full term. The exaggerated reduction in cerebral blood flow velocity in infants born at full term is caused by a simultaneous reduction in carbon dioxide tension that causes a comparatively large effect on the reduction of cerebral blood flow.

We thank Dr Kent Woods for statistical advice, and the nurses in the neonatal unit for their patience. DBS received financial support from the Spastics Society.

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Accepted 11 May 1988

Archives of Disease in Childhood, 1988, **63,** 1131–1136

Clinical factors associated with adverse outcome for babies weighing 2000 g or less at birth

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SUMMARY Using clinical factors, the probabilities of survival with and without major handicap were separately calculated by multiple logistic regression for 988 children who weighed 2000 g or less at birth and who were born in the period 1976–1980. For survivors weighing 501–1250 g in whom incidence of serious handicap was 21%, neonatal fits and the need for mechanical ventilation carried significantly increased risks of later serious handicaps. In contrast, for survivors weighing 1251–2000 g in whom the incidence of serious handicap was 6%, significant factors were spontaneous, uncomplicated preterm delivery, recurrent apnoea, and abnormal neonatal neurological findings. The probability of dying was assessed in two ways—firstly, using seven clinical factors available on admission to the neonatal unit, and secondly, using 10 perinatal and neonatal factors. Handicapped survivors had a perinatal risk between that of those babies who survived and that of those who died. Of the handicapped survivors, those with spastic diplegia and hemiplegia had been extremely low risk babies (medians 1·4% and 1·6%, respectively), whereas those with other impairments had much higher risks (range 17·5–38·1%). We postulate that certain impairments arise independently of clinical events, although most occur in children who had complicated perinatal courses.

The aetiology of the neurodevelopmental handicaps that occur in children with low birth weights who survive is poorly understood. Such handicaps comprise several different impairments affecting motor, sensory, and intellectual function. The many different combinations of impairment that are found suggest common predisposing factors. It has been postulated that those perinatal events that lead to a child being handicapped may be similar to those that culminate in death,[1] but similar impairments may be found among other children who have had no perinatal problems. This paper examines the hypothesis that handicap may be predicted from the clinical course of a low birthweight baby. Clinical factors associated with adverse perinatal outcome are defined in a group of babies who were born weighing 2000 g or less and who were managed in one perinatal referral centre during a five year period.

Subjects and methods

We studied 1034 consecutive babies weighing 2000 g or less, born between 1 January 1976 and 31 December 1980 who were cared for on the neonatal medical unit at this hospital. Seven hundred and nineteen were born here, and 315 were neonatal referrals. Details of the neurodevelopmental outcome of the survivors had been discussed elsewhere.[2 3] For the purposes of this study a neurodevelopmental handicap was defined as one or more of the following: cerebral palsy, developmental retardation (Griffiths quotient or Wechsler preschool and primary intelligence quotient (IQ) <71), blindness or deafness sufficient to warrant special education and hydrocephalus. The outcome was known at a median age of 39 months (range 24–81) for 702 of 724 babies who had been discharged (97%). Twenty had died (eight with considerable pre-existing handicaps), and 57 long term survivors had handicaps.

Patients were excluded if a serious congenital abnormality was clearly the cause of death (n=40) or handicap (n=10).[3] Factors associated with survival were therefore analysed for 270 babies who died in hospital and 714 survivors. The follow up data for

65 survivors was incomplete; these were excluded and factors associated with handicap were analysed for 594 healthy survivors and 55 with handicaps.

Information about the perinatal events and necropsy findings was retrospectively abstracted from the clinical records and coded for computer analysis. Preliminary analysis was done with the Statistical Package for the Social Sciences (SPSS). Thirty seven clinical factors were selected for further study. The incidence of perinatal death and handicap for children with each clinical factor is shown in table 1. Birth weight and gestational age were included as continuous variables in each analysis.

To examine the associations between each of these 37 factors, firstly with survival, and secondly with the presence of severe handicap among the survivors, a series of multivariate logistic regression analyses were carried out using the Genstat statistical package. These models associated the log odds (logit) of death or handicap with the factors under consideration and determined the strongest associations. To remove factors that were not significant from the models we adopted a 'backwards stepwise' approach; at each step the factors that contributed least to the 'fit' of the model were dropped as long as the actual difference made was not significant (p>0·05, according to the change in 'deviance'). Only babies with complete data could be included in this analysis. Once a final list of factors had been obtained, all babies with complete data on the final list of factors were included and the significance of each factor in turn was obtained by deleting it and examining the change in deviance.

It was not practicable to look for associations with individual impairments among the survivors, because of the small numbers, and so the log odds of severe handicap of any form were modelled. This was done for birth weights of 500–1250 g and 1251–2000 g so that we could compare the findings with our previous studies in which patients were divided into two groups—very low birth weight with high mortality and morbidity, and low birth weight with low mortality and morbidity.

A final analysis was performed to model log odds of death, firstly using data available at the time of admission to the neonatal medical unit, and secondly using neonatal variables as well. From the final model the predicted probability of death was calculated for each baby, separating those who died from those who survived, with and without handicap.

Results

FACTORS ASSOCIATED WITH NEURODEVELOPMENTAL HANDICAP AMONG SURVIVORS

Of the 124 children weighing from 500–1250 g at birth, 93 had complete records for all clinical factors and a further 20 were added at the final step; the incidence of handicap was 24 of 113 (21%). Two factors were significantly associated with subsequent handicap—neonatal fits and the need for mechanical ventilation (p<0·005 and p<0·025, respectively). Both were associated with increased risks of handicap with odds ratios of 5·7:1, 95% confidence interval (CI) 1·4 to 23, and 4·4:1, CI 1·5 to 13, respectively.

Of the 590 children weighing from 1251–2000 g at birth, 466 had complete records and a further 70 were added at the final step. The incidence of handicap in these children was 31 of 536 (6%). The factors most significantly associated with handicap were an uncomplicated spontaneous delivery, (odds ratio 2·9:1, CI 1·3 to 6·6, p<0·025), neonatal neurological abnormality (odds ratio 6·1:1, CI 2·3 to 16 p<0·001) and recurrent apnoea (p<0·005). Children with recurrent apnoeic spells were grouped by the time of onset and presence of respiratory distress (table 1), each group being compared with a group of children without apnoea. There were no impairments among the children who developed apnoea in the presence of established respiratory distress. Children who had early apnoea (within 3 days) had an increased risk (odds ratio 2·2:1, CI 0·6 to 7·8), as did children with late apnoea (odds ratio 4·3:1, CI 1·6 to 11·3).

CLINICAL FACTORS ASSOCIATED WITH DEATH

We analysed the data available up to the point of admission to the neonatal medical unit for 803 children with complete records. These comprised antenatal factors, details of delivery and resuscitation, birth weight, and gestational age, and including those babies who died in the delivery room. At the final step 146 children were added log odds of dying were calculated for those factors significantly associated with death (table 2). Decreasing birth weight was the factor with the strongest and most significant association, each 100 g below 2000 g increasing the risk of dying by a factor of 1·35. Neonatal transfer was associated with a three times increased risk, but this referred group is highly selected and the reasons for high mortality have been discussed elsewhere.[4] The small number of black babies in the study have less risk than white babies. Suppression of labour with sympathomimetic drugs was associated with a considerably reduced risk, but paradoxically those pregnancies complicated by more than one episode of preterm labour had an increased risk. It would therefore seem that merely delaying labour may be beneficial, but that stopping premature labour is not. Delay in the establishment of spontaneous respiration and the need for alkali at resuscitation (both indicative

Table 1 *Perinatal factors selected for multiple regression analysis*

Clinical factor	*Total No*	*No (%) who died*	*No (%) of healthy survivors*	*No (%) handicapped*
	988	274 (28)	659 (67)	55 (6)
Preconceptional:				
Ethnic group:				
White	871	243 (28)	579 (67)	49 (6)
Black	28	3 (11)	22 (79)	3 (11)
Asian	84	26 (31)	55 (66)	3 (4)
Social class:				
I+II	170	46 (27)	112 (66)	12 (7)
III	351	72 (21)	262 (75)	17 (5)
IV+V	154	42 (27)	102 (66)	10 (7)
Single mother	172	41 (24)	125 (73)	6 (4)
Previous obstetric loss:				
First trimester only	300	90 (30)	193 (64)	17 (6)
Any (including neonatal deaths;	122	23 (19)	88 (72)	11 (9)
Investigated for infertility	49	17 (35)	31 (63)	1 (2)
Antenatal:				
Pre-eclampsia	186	36 (19)	142 (76)	8 (4)
Antepartum haemorrhage (requiring intervention)	63	24 (38)	37 (59)	2 (3)
Preterm rupture of membranes (primary event)	265	69 (26)	178 (67)	18 (7)
Duration of ruptured membranes:				
12–24 hours	52	14 (27)	31 (60)	7 (14)
>24 hours	188	54 (29)	124 (66)	10 (5)
Multiple episodes of preterm labour	291	97 (33)	177 (61)	17 (6)
β agonists (>12 hours before delivery)	272	62 (23)	190 (70)	20 (7)
Steroids (>24 hours before delivery)	130	25 (19)	98 (75)	7 (5)
Preterm labour only (no recorded intervention or complication)	182	59 (32)	106 (58)	17 (9)
Antenatal referral to St Mary's Hospital	88	21 (24)	61 (69)	6 (7)
Delivery details:				
Route of delivery:				
Breech	140	64 (46)	64 (46)	12 (9)
Caesarean section	340	69 (20)	257 (76)	14 (4)
Intubated at delivery	383	152 (40)	211 (55)	20 (5)
Alkali given	229	101 (44)	117 (51)	11 (5)
Spontaneous respirations established after 10 minutes	70	30 (43)	37 (53)	3 (4)
Ventilated to neonatal unit (no respiratory effort)	109	82 (75)	24 (22)	3 (3)
Apgar score at 1 minute <7	533	192 (36)	311 (58)	30 (6)
Apgar score at 5 minutes <7	243	118 (49)	112 (46)	13 (5)
Small for dates (<10 th percentile)	320	58 (18)	250 (78)	12 (4)
Multiple pregnancy (No of babies)	173	45 (26)	116 (67)	12 (7)
Female	458	131 (29)	307 (67)	20 (4)
Neonatal transfer	306	139 (45)	143 (47)	24 (8)
Neonatal factors:				
Hyaline membrane disease	358	119 (33)	209 (58)	30 (8)
Apnoea:				
<72 hours old (no respiratory distress)	67	16 (24)	41 (61)	10 (15)
>72 hours old	110	21 (19)	72 (66)	17 (16)
With respiratory distress	122	63 (52)	54 (44)	5 (4)
Mechanical ventilation (>4 hours)	409	246 (60)	134 (33)	29 (7)
Pulmonary airleak	161	113 (70)	40 (25)	8 (5)
Pulmonary haemorrhage	34	30 (88)	4 (12)	0 —
Positive blood cultures	357	98 (28)	227 (64)	32 (9)
Meningitis	17	14 (82)	1 (6)	2 (12)
Symptomatic hypoglycaemia	66	26 (39)	37 (56)	3 (5)
Fits	85	50 (59)	23 (27)	12 (14)
Other neurological abnormality	146	87 (60)	43 (30)	16 (11)
Exchange transfusion:				
n=1	93	28 (30)	58 (62)	7 (8)
n=2–11	113	44 (39)	57 (50)	12 (11)

of perinatal asphyxia) were also associated with increased risk.

For the next analysis neonatal factors were included, but babies who died in the delivery suite were excluded. One hundred and sixty eight children were added at the final step making a total of 971. The factors most strongly associated with death are shown in table 3. Birth weight, recurrent preterm labour, and drug suppression of labour with drugs were again important, but the introduction of neonatal factors reduced the significance of the markers of asphyxia given above. Of the neonatal factors, mechanical ventilation conferred the highest risk, followed by neonatal meningitis, pulmonary haemorrhage, neurological abnormality, and pulmonary air leaks. Conversely, recurrent apnoea and septicaemia diagnosed microbiologically were associated with decreased risks of death. Because these latter variables are found among older neonates, the data set was re-examined controlling for age at death (grouped as less than 4 days and more than 3 days); the same factors remained associated with death.

Finally the predicted probability of death was calculated (based on the modelled log odds described in table 3) for the 971 babies admitted to the neonatal medical unit on whom complete data was available. This included 54 handicapped survivors, there being inadequate clinical records for one handicapped child who was born in 1977 with severe developmental delay and who had had a complicated neonatal course. The distribution of risks expressed as the percentage probability of dying is shown in table 4. The handicapped children have

Table 4 *Predicted probabilities of death for all patients with complete information*

	No	*% Probability of death*	
		Median	*Quartiles*
Babies who died	268	81·4	58·5–99·6
Survivors:			
No handicap	584	3·6	1·8–7·6
Handicap	54	11·7	2·9–40·0

Table 2 *Clinical factors associated with death: data available on admission to Neonatal Medical Unit (n=949)*

	p Value	*Odds ratio*	*95% Confidence interval*
Birth weight*	<0·001	1·35:1	1·3 to 4·0
Delayed onset of respirations:	<0·001		
>10 minutes		1·5:1	0·8 to 2·9
Ventilated from birth		7·7:1	4·2 to 14
Several episodes of preterm labour	<0·001	5·3:1	3·1 to 9·4
Neonatal transfer to St Mary's Hospital	<0·001	3·2:1	2·1 to 4·7
Alkali given at resuscitation	<0·01	1·9:1	1·2 to 3·2
β agonist given	<0·001	1:6·9	3·7 to 12·7
Ethnic group:	<0·025		
Black		1:9·5	1·3 to 68
Asian		1:1·3	0·7 to 2·5

*Risk increases at each decrease of 100 g.

Table 3 *Perinatal and neonatal factors associated with death (n=971)*

	p Value	*Odds ratio*	*95% confidence interval*
Birth weight*	<0·001	1·5:1	1·4 to 1·6
Mechanical ventilation	<0·001	32:1	17 to 62
Meningitis	<0·001	28:1	4·7 to 166
Pulmonary haemorrhage	<0·001	10:1	2·2 to 47
Neurological abnormality	<0·001	3·7:1	2·0 to 6·7
Multiple episodes of preterm labour	<0·001	4·2:1	2·1 to 8·4
Pulmonary air leak	<0·005	2·0:1	1·1 to 3·4
β agonist given	<0·005	1:3·1	1·5 to 6·5
Apnoeic spells:	<0·001		
After third day		1:5·9	3·0 to 11
Before third day, with respiratory distress syndrome		1:1·8	0·9 to 3·6
Pathogen isolated on blood culture	<0·001	1:5·1	3·1 to 9·5

*Risk increases at each decrease of 100 g.

Table 5 *Predicted probabilities of death: individual impairments*

	No	*% Probability of death*	
		Median	*Quartiles*
Spastic diplegia	14	1·4	0·5–3·6
Spastic hemiplegia	7	1·6	0·8–34·0
Spastic quadriplegia	10	17·5	3·2–44·0
Developmental retardation*	9	12·8	0·7–55·1
Blindness	7	20·6	20·6–55·1
Hydrocephalus	9	34·0	17·5–48·9
Deafness	7	38·1	12·4–87·6

*As only impairment.

predicted probabilities between those of the non-handicapped survivors and those of the babies who died, but with considerable overlap among the survivors. When individual impairments are considered (table 5), this overlap is mainly among the children with diplegia and hemiplegia. Children with either of these two cerebral palsies have lower probabilities than those children with quadriplegia (Mann-Whitney U test: $p=0\cdot003$ and $p>0\cdot1$, respectively). All other groups have comparatively high predicted probabilities of death when compared with non-handicapped suvivors, or with those with either diplegia or hemiplegia.

Discussion

Although the origins of most neurodevelopmental impairments among survivors with low birth weights remain obscure, these data show that most impairments were found in children who had complicated perinatal courses. Small numbers in each group precluded multivariate analysis of associated factors with individual impairments, but the high frequency and similarity of neonatal problems encountered by children with such diverse impairments (such as blindness or cerebral palsy) and the frequent coexistence of such impairments[3] encouraged us initially to analyse the 'handicap' group as one.

Neonatal referrals, who comprised of those with handicaps 24 (44%), were included because almost all had been delivered in district general hospitals and stabilised before transport. When allowance was made for the need for mechanical ventilation, survival and incidence of handicap were similar in patients born here and those who had been referred.[4]

Although dividing the survivors into two groups according to birth weight (less than 1251 g and more than 1250 g) seems an artificial distinction, analysis of the associates of handicap among the survivors in the two groups was suggested by our finding of different ranges of impairments in the two groups,[3] differing individual associations with handicaps,[2] and—most importantly—a considerable increase in mortality and handicap in those who weighed less than 1251 g.[3]

The association between impairment of the neurological and respiratory systems and outcome is to be expected. They are the systems most frequently compromised in the neonatal period, and among the 222 (72%) of the babies in the study who died and had necropsies, 180 (81%) had hyaline membrane disease and 162 (73%) had intraventricular haemorrhages (unpublished observations). Most of these children were born before cerebral ultrasound scanning became standard in this hospital and thus the association of impairment with such findings could not be explored.

The small number of factors associated with handicap was disappointing but confirmed other reports, mainly from studies of babies weighing less than 1000 g, which have variously associated low Apgar scores,[5] mechanical ventilation,[6 7] fits,[5 8] and clinical or ultrasound evidence of intraventricular haemorrhage.[8] A further study attempted to correlate cerebral palsy or developmental retardation with clinical factors in babies weighing less than 1501 g from two separate hospitals.[9] No common associated factors were found. Furthermore, it was observed that only half of the 30 children with cerebral palsy had been ventilated and only two (7%) had an Apgar score at five minutes of less than four. Thus children with cerebral palsy were not necessarily the illest babies. In a case control study of 18 preterm children with diplegia, an Apgar score of less than four at one minute was found more often among diplegic children, who were also more likely to have had symptomatic intracranial haemorrhages or neonatal fits.[10] Fourteen diplegic children (78%) had little or no respiratory distress, however, and similar proportions had no evidence of intracranial haemorrhage (72%), or seizures (78%).

In this study 11 handicapped children (20%) did not need neonatal intensive care. These were four children with diplegia, four with hemiplegia—both impairments with a low calculated risk of death—one with tetraplegia, and two with developmental retardation. Low Apgar scores at one minute were, however, found in six of 14 children with diplegia (43%) and three of seven children with hemiplegia (43%). In contrast, only one of 10 children with quadriplegia had an uncomplicated neonatal course (he later developed infantile spasms) and only two had low Apgar scores at one minute. Babies who developed diplegia and hemiplegia later were not, therefore, necessarily ill in the neonatal period. These unexplained impairments may have their origin in the antenatal or perinatal periods, as indicated by depressed Apgar scores at birth and a low incidence of perceived perinatal complications. In contrast, in this study, quadriplegia was found mainly in children who developed serious postnatal illness and who had seemed to be in good condition at birth.

Certain impairments that often coexist—quadriplegia, blindness, and deafness—are more common among the smallest babies and occur in those needing intensive care and mechanical ventilation, often with associated neurological abnormality. A similar distribution of birth weights and incidence of neonatal factors is found in posthaemorrhagic hydrocephalus, which we also defined as a serious impairment. Recent developments in neonatal care resulting in improved survival for the smallest babies may therefore be associated with the presence of severe multiple handicaps in survivors.

The sole antenatal factor that could be associated with later handicap was an otherwise uncomplicated spontaneous delivery in the group weighing 1251–2000 g at birth. Surprisingly, antepartum haemorrhage, pre-eclampsia, preterm rupture of the membranes, or antenatal transfer seemed to have no effect. When factors associated with death were examined, however, a beneficial effect of delaying labour for more than 12 hours with sympathomimetic drugs was found but there was an adverse effect if there was more than one isolated episode of preterm labour. The use of sympathomimetic drugs is controversial[11]; it has been claimed that β receptor agonists may reduce the subsequent incidence of hyaline membrane disease in the baby.[12 13] A reduction in mortality, such as is implicit here, would be the logical result. The aim of tocolysins, however, is to stop preterm labour. These data suggest that delayed delivery may be beneficial, whereas more than one discrete episode of preterm labour seems to be undesirable.

Birth weight was more important in predicting outcome in these babies than either gestational age itself or being small for gestational age, neither of which exerted any significant extra effect. In addition, neither gender nor route of delivery had any effect on outcome, as previously reported.

Although the condition of the baby at delivery was not associated with later handicap, asphyxia sufficient to delay the onset of spontaneous respiration by more than 10 minutes or to warrant the use of alkalis at resuscitation was associated with increased mortality, stressing the need for antenatal detection and prevention of asphyxia. These factors disappear when neonatal data are added to the model, their effect being swamped by the stronger association of adverse neonatal variables.

There is an increased predicted probability of death among handicapped survivors during the perinatal period, and the possible origin of some impairments in the antepartum period confirm this. Recent work has extended the observation of Sameroff and Chandler[14] that this extends beyond conception and delivery into the socioenvironmental factors that are associated with low birth weight, and which exert influence on later development.[15]

This project was supported by Birthright National Fund for Childbirth Research.

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Accepted 11 April 1988

Archives of Disease in Childhood, 1988, **63,** 1137–1145

Echocardiographic diagnosis of fetal heart defects in mid trimester

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SUMMARY One hundred and thirty five consecutive fetuses of between 16 and 23 weeks' gestation that were considered to be at high risk of having structural heart defects were examined prospectively to determine the reliability of echocardiography for diagnosing such defects in mid timester. Each echocardiogram was done in a standard manner and cardiac anatomy was analysed segmentally. Twelve fetuses were excluded from analysis because of lack of follow up. Of the remaining 123 fetuses, 109 had no evidence of heart disease when followed up. In this group the prenatal echocardiogram was normal in 105 and technically inadequate in four; thus there were no false positive diagnoses of heart disease in fetuses subsequently shown to have normal hearts. Fourteen had heart defects at follow up. The serious defect was correctly diagnosed prenatally in 10 of 14 cases, whereas in the other four the prenatal echocardiogram was considered normal. Some errors were made in diagnosing associated segmental defects particularly if the heart disease was complicated. Therapeutic abortion was carried out in seven cases; in five of the fetuses the prenatally diagnosed heart defect was the sole or an important contributing reason for the abortion. We conclude that echocardiography is a reliable method for diagnosing many heart defects in the mid trimester.

Ultrasonography has become a valuable and reliable technique for prenatal diagnosis of many fetal abnormalities.[1 2] Techniques have been described for performing prenatal two dimensional,[3–6] as well as M mode,[5–8] and Doppler[9 10] echocardiography. These investigations have shown that prenatal echocardiography can identify normal cardiac anatomy at gestational ages ranging from about 17 weeks to full term. Many structural heart defects have been diagnosed in older fetuses[11–15] with echocardiography, but there are few reports of the prospective diagnosis of heart defects in fetuses of less than 24 weeks' gestation.[6 13 16–18] The accuracy of prenatal echocardiography has not been prospectively evaluated for the diagnosis of complex cardiac defects segment by segment, yet management of pregnancies at high risk of congenital heart defects requires diagnostic methods that are reliable at a stage of gestation when the option of terminating the pregnancy is still available.

We investigated the use of prenatal echocardiography for diagnosing structural heart defects in fetuses of less than 24 weeks' gestation in a population considered at high risk of congenital heart disease.

Subjects and methods

Between December 1982 and July 1986 we examined 135 consecutive fetuses of less than 24 weeks' gestation in 133 pregnancies. Eighty examinations were done at the Children's Hospital, Boston, 41 were at West Virginia University Hospital (December 1982 to June 1985), and nine at the Medical Center Hospital of Vermont (July 1985 to June 1986). Five fetuses underwent a second examination either as a follow up for hydrops or because the first examination was technically inadequate. Twelve fetuses were excluded from the study: nine were lost to follow up, two died in utero and did not undergo necropsy, and one was therapeutically aborted without necropsy. The gestational ages of the 123 included in the study ranged from 16 to 23 weeks at the time of examination (mean 20·5).

Risk factors prompting referral for prenatal echocardiography included: family history of congenital heart defect,[19–21] maternal diabetes,[22] maternal exposure to teratogenic agents during early gestation,[23] chromosomal abnormalities or multiple congenital anomalies detected by prenatal screening,[24] a congenital heart defect suspected on obstetric ultrasound examination, and fetal arrhythmias.

All examinations were done by three of the authors (IAP and SPS at the Children's Hospital, Boston, and SBY at West Virginia University Hospital and the Medical Center Hospital of Vermont). Prenatal echocardiograms were done with an ATL Mark 600 or Hewlett Packard cardiac imager equipped with a short or medium focus 5·0 mHz transducer. Two dimensional echocardiographic imaging was supplemented by two dimensional directed M mode or Doppler cardiography, or both, in patients with abnormal rhythms or anatomy. Examinations were recorded on 1/2" video cassette tape for review in real time, slow motion, and stop frame modes.

The examination was done with the mother supine or in a lateral decubitus position. If the position of the fetus was unfavourable for cardiac imaging, the mother was asked to change position or walk about the laboratory. If the position could not be improved, the patient was asked to return on another day for examination.

Each examination was done in a standard manner. The position and orientation of the fetus was determined using long and short axis scans of the fetal trunk.[3] The fetal cardiovascular anatomy was then analysed segment by segment as previously described in neonates.[25–27] Visceroatrial situs was calculated from a transverse view of the abdomen near the diaphragm by evaluating the respective positions of the inferior vena cava, the descending aorta, and the spine, as well as the pattern of the venous connections (fig 1).[28] Long and short axis views of the trunk were used to provide short and long axis views, respectively, of the fetal heart.[3] A modified long axis view of the trunk was used to visualise the aortic arch.[3] Using these views, the veins, atriums, atrial septum, atrioventricular valves, ventricles, ventricular septum, semilunar valves, and great arteries were sequentially scanned in at least two orthogonal planes.

The recorded examination was reviewed and an anatomical diagnosis assigned using the nomenclature proposed by VanPraagh *et al*.[29] If any examination failed to visualise any cardiac segment adequately, the study was considered technically

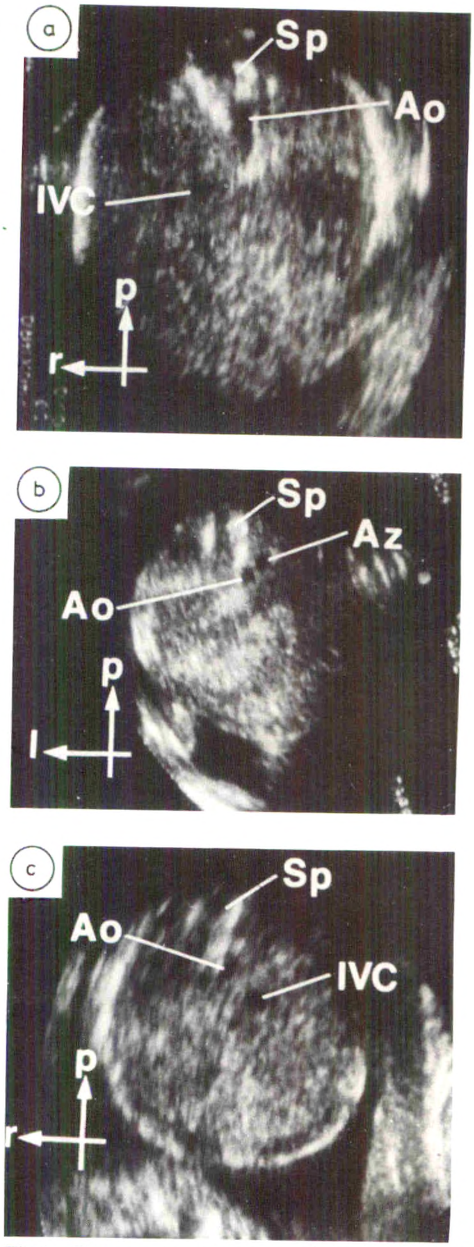

Fig 1 *Transverse sections of the fetal trunk at the level of the diaphragm showing the relative positions of the aorta, inferior vena cava and spine. a—Case 2. Note the right anterior position of the inferior vena cava and the left posterior position of the aorta. b—Case 8 (heterotaxy). A dilated azygos vein is posterior to the aorta associated with absence of the renal to hepatic segment of the inferior vena cava. c—Case 9. Because of a left diaphragmatic hernia, the aorta and inferior vena cava are juxtaposed to the left of the spine (similar to asplenia). Ao: aorta, Az: azygos vein, IVC: inferior vena cava, l: left, r: right, Sp: spine, and p: posterior.*

inadequate. Because, however, it was often difficult to see pulmonary venous connections and the aortic isthmus clearly, studies that defined these structures indistinctly were considered technically adequate. Technically inadequate examinations are reported as such and were not excluded from analysis.

The result of each prenatal echocardiogram was discussed with the parents, the referring obstetrician, and (if concerned) the paediatric cardiologist. The presumed limitations of the test, specifically for the diagnosis of atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, and minor abnormalities of the valves were discussed with the parents before the examination and again afterward in those cases in which no abnormality was detected.

If a cardiac defect was diagnosed, the nature of the defect including anatomy, physiology, prognosis, and possible postnatal treatment was explained to the parents and physicians. The parents and primary physicians were encouraged to contact us again after the examination if questions arose. The decision to continue or terminate the pregnancy was made by the parents in consultation with the primary physician. If the pregnancy was continued the parents were referred to a paediatric cardiologist who made appropriate plans for perinatal management.

The outcome of live births was found out by telephone interview with a parent or primary physician, or both, one month to one year postnatally. The infant was considered normal if there were no findings suggestive of a congenital heart defect at routine paediatric physical examination (n=109). All infants with clinically suspected cardiac defects were examined by a paediatric cardiologist. The results of clinical examination, two dimensional echocardiography, cardiac catheterisation, and angiography or surgical inspection, or both, were obtained in these eight cases. Necropsy reports were obtained in all 10 cases in which the examination was performed.

Results

In 109 cases there was no evidence of congenital heart disease at follow up. In 105 of these the prenatal echocardiogram was normal, and in the other four cases the examination was technically inadequate.

Fourteen of 123 (11%) were confirmed to have heart defects either at clinical follow up or at necropsy. A cardiac defect had been diagnosed prenatally in 10 of the 14 cases. Six of these 10 were therapeutically aborted and one fetus died in utero at 33 weeks' gestation with severe hydrops fetalis. Of the remaining three infants who were born alive, two died in the neonatal period—one of the heart defect and the other of neonatal hepatitis. The third died at the age of 2½ months after a viral infection. Necropsy confirmed the serious heart defects diagnosed by prenatal echocardiography in all 10 cases. Serious defects that were diagnosed were: Ebstein's anomaly (n=1), tricuspid regurgitation (n=1), pulmonary stenosis with hypoplastic right ventricle (n=1), tetralogy of Fallot with pulmonary atresia and complete common atrioventricular canal (n=1), hypoplastic left heart syndrome (n=2), and complex heart disease with heterotaxy (n=3) (table 1).

Defects were not diagnosed prenatally in four of the 14 fetuses that were subsequently found to have congenital heart defects (table 2). The lesions in those four cases were: patent ductus arteriosus (n=1), moderate sized apical muscular ventricular septal defect (n=1), midmuscular ventricular septal defect (n=1), short segment coarctation of the aorta (n=1), and atrial septal defect secundum (n=1). In the infant with persistent patent ductus arteriosus spontaneous closure occurred when a few weeks old. The infant with coarctation and ventricular septal defect had the coarctation repaired when 3 weeks old, and the ventricular septal defect subsequently closed spontaneously. The other infant with a ventricular septal defect (age 12 months) does not at the time of writing seem to require operation. The atrial septal defect secundum was an incidental finding at necropsy following therapeutic abortion for other abnormalities.

The parents of four fetuses with prenatally diagnosed heart defects chose to continue the pregnancies after counselling. Two of these fetuses (cases 4 and 7) were born alive but died in the neonatal period despite management of the heart defects. A third fetus (case 6) died in utero at 33 weeks' gestation of fetal hydrops. The remaining fetus (case 10) was born at full term and underwent palliative ligation of patent ductus arteriosus and pulmonary artery banding. The infant subsequently developed pneumonia and died when 2½ months old.

Discussion

In our study, adequate two dimensional echocardiograms were obtained in 97% of fetuses before 24 weeks' gestation. We correctly excluded structural heart defects in all fetuses that were subsequently found to be normal and in which technically adequate echocardiograms could be obtained; no normal fetus was diagnosed as having a structural heart defect by prenatal echocardiography.

Table 1 *Heart defects diagnosed prenatally*

Case No	*Gestational age (weeks)*	*Indication for examination*	*Echocardiographic diagnosis*	*Final diagnosis and method of confirmation*
1	21	Potter's syndrome on ultrasonography Fetal hydrops	1 {S,D,S}* 2 Tricuspid regurgitation with dilated right atrium 3 Probable pulmonary stenosis	*Therapeutic abortion (necropsy)* 1 {S,D,S}* 2 Dilated right atrium 3 No pulmonary stenosis 4 Potter's syndrome
2	21	Abnormal heart on routine ultrasonography	1 {S,D,S}* 2 Severe Ebstein's anomaly 3 Tricuspid regurgitation with dilated right atrium 4 Severe pulmonary stenosis or atresia	*Therapeutic abortion (necropsy)* 1 {S,D,S}* 2 Severe Ebstein's anomaly 3 Dilated right atrium 4 Moderate stenosis of pulmonary valve
3	19	Abnormal heart on routine ultrasonography Other abnormalities	1 {S,D,S}* 2 Tricuspid regurgitation 3 Mild right ventricular hypoplasia 4 Infundibular and valvular pulmonary stenosis 5 Hypoplastic pulmonary arteries	*Therapeutic abortion (necropsy)* 1 {S,D,S}* 2 Dilated right atrium 3 Mild right ventricular hypoplasia 4 Infundibular and valvular pulmonary stenosis 5 Hypoplastic pulmonary arteries 6 Atrial septal defect secundum 7 Skeletal, gastrointestinal, genitourinary, and facial abnormalities
4	20	Previous child with congenital heart disease	1 {S,D,S}* 2 Hypoplastic right ventricle 3 Pulmonary atresia with hypoplastic pulmonary arteries 4 Intact ventricular septum	*Neonatal death (necropsy)* 1 {S,D,S}* 2 Hypoplastic right ventricle 3 Pulmonary atresia with hypoplastic pulmonary arteries 4 Moderate membranous ventricular septal defect
5	18	Previous child with congenital heart disease	1 {S,D,S}* 2 Hypoplastic left heart syndrome 3 Mitral atresia 4 No left ventricle seen 5 Hypoplastic aorta	*Therapeutic abortion (necropsy)* 1 {S,D,S}* 2 Hypoplastic left heart syndrome 3 Mitral atresia 4 No left ventricle seen 5 Hypoplastic aorta 6 Critical aortic valvular stenosis
6	22	Abnormal heart on routine ultrasonography	1 {S,D,S}* 2 Hypoplastic left heart syndrome 3 Mitral atresia 4 Hypoplastic left ventricle 5 Aortic atresia 6 Hypoplastic ascending aorta	*Intrauterine death (33 weeks) (necropsy)* 1 {S,D,S}* 2 Hypoplastic left heart syndrome 3 Mitral atresia 4 Aplastic left ventricle 5 Aortic atresia 6 Hypoplastic ascending aorta
7	23	Maternal diabetes	1 {S,D,S}* 2 Atrial septal defect primum 3 Complete common atrioventricular canal 4 Tetralogy of Fallot 5 Long segment pulmonary atresia 6 No mediastinal pulmonary arteries seen	*Premature birth, hepatitis, neonatal death (necropsy)* 1 {S,D,S}* 2 Atrial septal defect primum 3 Complete common atrioventricular canal 4 Tetralogy of Fallot 5 Long segment pulmonary atresia 6 Severe hypoplasia of branches of pulmonary artery

Table 1 *Continued*

Case No	*Gestational age (weeks)*	*Indication for examination*	*Echocardiographic diagnosis*	*Final diagnosis and method of confirmation*
8	23	Abnormal heart on routine ultrasonography	1 {A,D,D}* Double outlet right ventricle 2 Heterotaxy 3 Interrupted inferior vena cava with azygous vein to superior vena cava 4 Common atrium 5 Complete common atrioventricular canal, right ventricle dominant 6 Left ventricular hypoplasia 7 Anterior large aorta 8 Hypoplastic pulmonary arteries	*Therapeutic abortion (necropsy)* 1 {A,D,D}* Double outlet right ventricle 2 Heterotaxy 3 Interrupted inferior vena cava with azygous vein to superior vena cava 4 Common atrium 5 Complete common atrioventricular canal, right ventricle dominant 6 Left ventricular hypoplasia 7 Anterior large aorta 8 Hypoplastic pulmonary arteries 10 Ipsilateral pulmonary venous connection 11 Infundibular and valvular pulmonary stenosis
9	21	Abnormal heart on routine ultrasonography Other abnormalities including left diaphragmatic hernia	1 {A,?,L}* Double outlet right ventricle 2 Heterotaxy (asplenia) 3 Inferior vena cava and abdominal aorta transposed to left 4 Pulmonary venous connection not seen 5 Common atrium 6 Common atrioventricular valve 7 Single right ventricle 8 Large anterior aorta 9 Valvular pulmonary stenosis with small pulmonary artery	*Therapeutic abortion (necropsy)* 1 {S,D,S}* Double outlet right ventricle 2 Nor confirmed 3 Right inferior vena cava transposed to left 4 Anomalous pulmonary venous connection to left vertical vein 5 Hypoplastic left atrium, dilated right atrium, atrial septal defect secundum 6 Mitral atresia, large tricuspid valve 7 Single right ventricle 8 Large anterior pulmonary artery 9 Subvalvular and valvular aortic stenosis 10 Left diaphragmatic hernia 11 Skeletal and neurological abnormalities
10	18	Fetal bradycardia	1 {A,?,N}* 2 Dextrocardia 3 No inferior vena cava seen 4 Common atrium 5 Dilated coronary sinus 6 Large atrioventricular canal type ventricular septal defect 7 Normally related great arteries	*Died at 2½ months (necropsy)* 1 {A,L,I}* 2 Dextrocardia 3 Interrupted inferior vena cava with azygous vein to right superior vena cava 4 Hypoplastic left atrium without venous connection 5 Dilated coronary sinus, also right superior vena cava 6 Moderate posterior muscular ventricular septal defect 7 Normally related great arteries

*Segmental notation described by VanPraagh *et al.*[29]

VanPraagh's segmental nomenclature[29]—The segmental set notation formulated by VanPraagh is a shorthand description of the situs or spatial organisation of the three major cardiac segments; the three letters enclosed in the brackets denote the situs of the atriums, ventricles, and great arteries, in that order. Atrial situs is designated solitus ("S"), inversus ("I"), or ambiguus ("A"). Ventricular situs, occupying the second position in the set, is described according to the direction of embryonic heart tube looping; dextro-loop ("D") in situs solitus and levo-loop ("L") in situs inversus. "S" or "I" in the last position denote solitus or inversus normally related great arteries, respectively. "D", "L", or "A" in the third position refer to the spatial orientation of the aortic valve and the pulmonary valve —that is, to the right, to the left, or directly anterior, respectively, in the setting of the various malpositions of the great arteries. The type of malposition of the great arteries cannot be inferred from the set notation and must be stated separately. The atrioventricular alignments (connections) may be inferred from the notation on the presumption that the alignments will correlate with the atrioventricular situs associations. For example, {S,D} and {S,L} imply concordant or discordant atrioventricular alignments, respectively, in atrial situs solitus. Disharmony between atrioventricular situs and alignments, which rarely occurs, must be stated. Ventriculoarterial alignments are concordant if the great arteries are normally related—that is { , ,S} or { , ,I}. Otherwise the ventriculoarterial alignments will be clear from the stated conotruncal malformation—for example, discordant in transposition of the great arteries or concordant in anatomically corrected malposition.

Table 2 *Heart defects not diagnosed prenatally*

Case No	*Gestational age (weeks)*	*Indication for examination*	*Echocardiographic diagnosis*	*Final diagnosis and method of confirmation*
11	20	Previous child with congenital heart disease	1 {S,D,S}* 2 No structural heart defects	*Born alive (angiography, echocardiography, clinical observation)* 1 {S,D,S}* 2 Moderate midmuscular ventricular septal defect 3 Severe short segment coarctation of aorta
12	20	Previous child with congenital heart disease	1 {S,D,S}* 2 No structural heart defects	*Born alive (echocardiography, clinical observation)* 1 {S,D,S}* 2 Moderate apical muscular ventricular septal defect
13	23	Fetal arrhythmia	1 {S,D,S}* 2 No structural heart defects	*Born alive (clinical observation)* 1 {S,D,S}* 2 Patent ductus arteriosus
14	20	Amniocentesis $46,3p^-$ Other abnormalities	1 {S,D,S}* 2 No structural heart defects	*Therapeutic abortion (necropsy)* 1 {S,D,S}* 2 Atrial septal defect secundum 3 Renal and skeletal abnormalities

*Segmental notation described by VanPraagh *et al.*[29]

Our results also show that many forms of congenital heart disease, including complex defects, can be diagnosed in fetuses before 24 weeks' gestation using two dimensional echocardiography. Thus the information necessary to make rational decisions about continuing or terminating pregnancies at high risk of congenital heart defects can be obtained in nearly all patients. In five of our cases the knowledge that the fetuses had severe heart defects was influential in the decision to terminate the pregnancy. In the three cases in which severe cardiac defects were diagnosed prenatally and the pregnancies were carried to full term, the family and responsible physician were prepared for the birth of an infant with congenital heart disease.

The three complex cases of heterotaxy illustrate both the potential for accurate segmental diagnosis and the potential for error in such an analysis. In case 8 a complex defect was correctly diagnosed in nearly all details. Persistent left superior vena cava and ipsilateral pulmonary venous connection were not seen prenatally (figs 1 and 2, and table 2). In case 9, though double outlet single right ventricle was correctly diagnosed, several errors were made in the segmental diagnosis. The inferior vena cava and descending aorta were to the left of the spine at the diaphragm suggesting visceroatrial heterotaxy (fig 1c). Displacement of the liver to the left by the left diaphragmatic hernia disorted the relationship between the inferior vena cava and spine in this fetus with normal visceroatrial situs. The anomalous pulmonary venous connection to the left vertical vein was not recognised prenatally. The hypoplastic left atrium with mitral atresia could not be seen adequately, and the dilated right atrium and tricuspid valve were misinterpreted as a common atrium and common atrioventricular valve. Functionally, the most important error was in mistaking the enlarged pulmonary artery and ductus arteriosus for a large aorta. We believe that this was partly a result of our heightened suspicion of asplenia (which is commonly associated with malposition of the great arteries and pulmonary stenosis), and partly because of the inability to resolve as separate structures the hypoplastic aorta and the ductus arteriosus (fig 3). In retrospect a branch pulmonary artery could be seen arising from the anterior vessel, identifying it as the pulmonary trunk. Though in this case the errors in diagnosis did not influence the management appreciably, some of the errors might be important if the heart disease were an isolated abnormality.

In case 10, our failure to identify the inferior vena cava led us to suspect that there was an interrupted inferior vena cava with azygous continuation, but this was not so. As in case 9, a hypoplastic left atrium was not recognised, and a dilated right atrium was misinterpreted as a common atrium. Visualisation of the atrioventricular valve and ventricular morphology was not good enough to identify the ventricular loop, and a posterior muscular ventricular septal defect was mistaken for an atrioventricular canal defect. In two additional fetuses (cases 1 and 2), tricuspid regurgitation seemed to restrict the excursion of the pulmonary valve resulting in an overestimation of the degree of obstruction.[30]

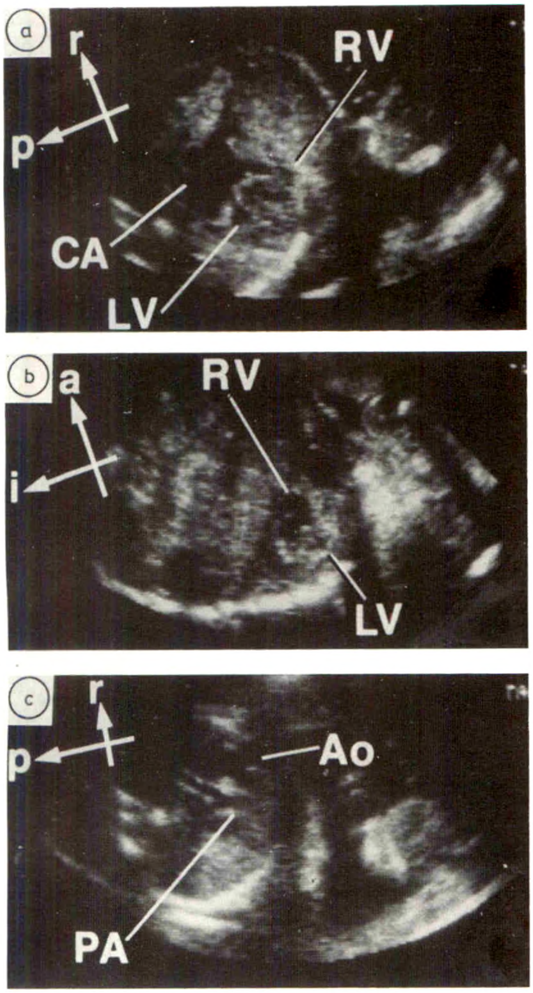

Fig 2 *Case 8 (heterotaxy). a—Four chamber view of the heart showing common atrium, common atrioventricular valve, and right ventricular dominance. b—Short axis view of the ventricles showing large right ventricle and hypoplastic left ventricle. c—Transverse cut through the great arteries showing large aorta and hypoplastic pulmonary arteries. a: anterior, CA: common atrium, i: inferior, LV: left ventricle, PA: pulmonary artery, RV: right ventricle, Ao: aorta, r: right, and p: posterior.*

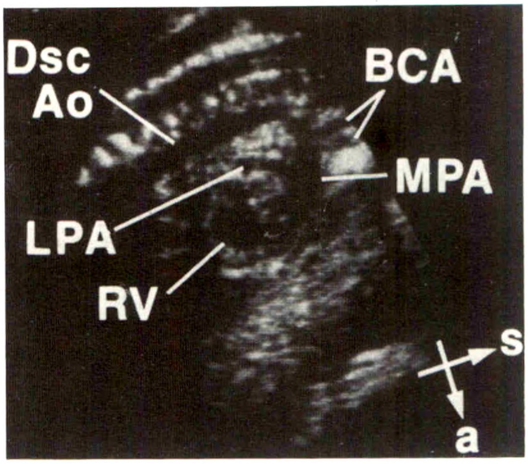

Fig 3 *Case 9. Parasagittal view in fetus with double outlet single right ventricle showing how the main pulmonary artery and ductus arteriosus can look like the aortic arch. Note the left pulmonary artery arising from the main pulmonary artery. BCA: brachiocephalic arteries, Dsc Ao: descending aorta, LPA: left pulmonary artery, MPA: main pulmonary artery, s: superior, RV: right ventricle, and a: anterior.*

In summary, diagnostic errors were made in the evaluation of each cardiac segment. Systemic and pulmonary venous anomalies, were particularly difficult to visualise in fetuses of less than 24 weeks' gestation, though improved resolution and new techniques (such as colour flow Doppler) may improve the sensitivity. On two occasions a small atrial chamber was not recognised and this led to a false diagnostic impression of a single atrium. In one case the presence of mitral atresia led to the misdiagnosis of a single common atrioventricular valve, and on two occasions imaging was not good enough to see ventricular looping. Evaluation of the infundibular and semilunar valve segments of the heart was largely successful, though in two cases the presence of severe tricuspid regurgitation influenced the assessment of the pulmonary valve.

Our experience suggests that some additional defects are unlikely to be diagnosed consistently by prenatal echocardiography, at least before 24 weeks' gestation. We missed muscular ventricular septal defects and coarctation of the aorta largely because of limitations in resolution of the imaging devices. None of these defects could be definitely diagnosed, even in retrospect. Other defects that might not be detected for the same reason include abnormalities of the valves such as bicommissural aortic valve or congenital mitral stenosis. Normal fetal physiology results in a widely patent foramen ovale, precluding reliable prenatal diagnosis of atrial septal defect secundum (fig 4). Prenatal echocardiography cannot predict postnatal patency of the ductus arteriosus, and in some cases coarctation of the aorta may develop postnatally in association with closure of the ductus arteriosus.[31]

Because a fetus with a normal two dimensional echocardiogram was not re-examined again, we cannot exclude the possibility that some defects missed at the first examination might be detected

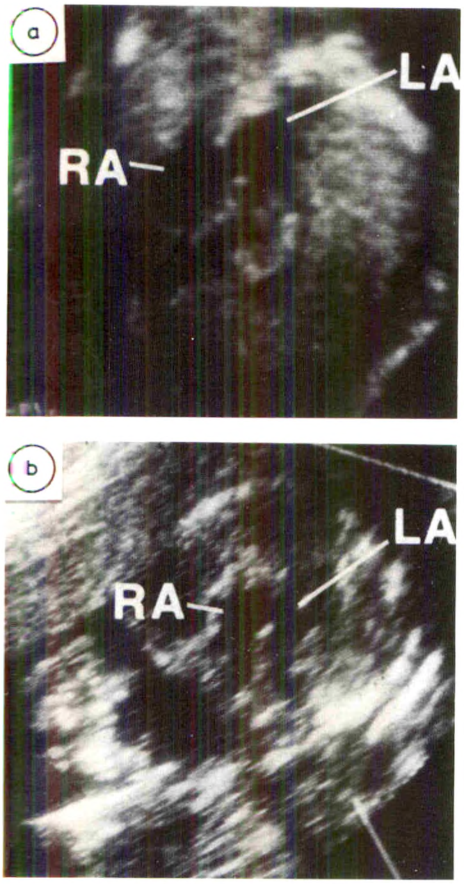

Fig 4 *Four chamber views of the heart illustrating the difficulty in diagnosing atrial septal defect secundum. a—Case 12 with intact atrial septum at follow up, and b—Case 14 with secundum atrial septal defect at necropsy. LA: left atrium, and RA: right atrium.*

later in gestation. None the less, most of the defects that might be difficult or impossible to diagnose using prenatal echocardiography can be treated surgically with low risk. It seems unlikely that parents would choose to terminate a pregnancy because of detection of one of these lesions.

Though the postnatal clinical evaluation used to establish normality in our patients is not proof of the absence of a heart defect, it is the most common way of detecting such defects. Abnormalities that may be missed by routine clinical examination in young infants include atrial septal defects, mild coarctation of the aorta, and minor valvular defects, all of which would be unlikely to be diagnosed by fetal echocardiography. Thus the clinical examination seems adequate to diagnose those lesions that one hopes to detect by prenatal echocardiography.

The high yield of cardiac defects in our series is the result of the highly selected nature of our patient population. The disproportionate number of fetuses with unusual and severe anomalies was largely because of referral after routine obstetric ultrasound examination had suggested the presence of a heart defect. Similar skewing of the distribution towards more severe lesions was noted in the series reported by Allen *et al.*[32]

Though prenatal echocardiography is a promising and useful technique, its limitations should be recognised. Reliable diagnosis of structural heart defects, especially complex lesions, in utero requires extensive knowledge of normal and pathological cardiac anatomy. Despite meticulous use of a segmental approach to prenatal echocardiographic diagnosis of structural heart defects we have been unable to achieve the diagnostic accuracy attainable postnatally. We hope that as techniques improve prenatal diagnosis will become as accurate as postnatal diagnosis.

This study was supported in part by training grant No 5T32HLO 752–03 from the National Institutes of Health.

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Accepted 26 May 1988

Archives of Disease in Childhood, 1988, **63,** 1146–1150

Neonatal outcome after prolonged rupture of the membranes starting in the second trimester

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SUMMARY The neonatal outcomes of 30 pregnancies that were complicated by premature an prolonged rupture of the membranes that had started in the second trimester of pregnancy, wer reviewed. The neonatal mortality was 11 (36%), the main cause of death being pulmonar hypoplasia. Two infants died of sepsis, but these were the only proved episodes of maternal o fetal infection. Of the survivors 27% developed compressive limb abnormalities, all of whic responded to passive physiotherapy. Pulmonary hypoplasia was significantly associated wit earlier onset of rupture of the membranes, and the absence of fetal breathing movements Compressive limb abnormalities were significantly associated with longer periods of oligohydramnios. We conclude that premature rupture of the membranes, even with onset in the secon trimester, may be associated with a favourable outcome and this may be predicted by th persistence of fetal breathing movements. We therefore, recommend expectant management o such pregnancies, but suggest elective delivery at 34 weeks to limit fetal exposure to uterin compression and minimise the risks of prematurity.

Premature rupture of the membranes is a common complication of pregnancy.[1] When it occurs in the second trimester the prognosis is poor,[2] and as a consequence termination of the pregnancy is often recommended. The neonates may have pulmonary hypoplasia, altered facies, and aberrant limb development (Potter's syndrome).[3] Premature rupture of the membranes permits chronic drainage of amniotic fluid resulting in oligohydramnios, so such abnormalities may be the result of prolonged compression of the fetus by the uterus in the absence of the usual 'cushion' of amniotic fluid.[4] Pulmonary hypoplasia has been reported after oligohydramnios of only six days' duration,[5] but it has been suggested that compressive abnormalities are more likely to develop after chronic reduction in the amount of amniotic fluid.[2] Our preliminary report, however, included normal survivors of pregnancies complicated by severe oligohydramnios that had existed for as long as 17 weeks.[6]

The aim of the present study was to follow prospectively a larger series of pregnancies complicated by prolonged rupture of the membranes that had started in the second trimester in an attempt to find out the neonatal mortality and morbidity. We hoped to determine the association between the onset and duration of rupture of the membranes and mortality and morbidity, and find out if the persistence of fetal breathing movements is a reliabl indicator of favourable neonatal outcome.[6]

Patients and methods

During a period of one year all pregnancies wit rupture of the membranes of longer than two week duration occurring in the second trimester wer eligible for entry into the study. The various option in management and the prognosis of pregnancie complicated by premature rupture of the membrane were carefully explained to the patients referred t our unit and their partners. If a patient then decide to be treated expectantly she was entered into th study.

The patient was admitted to the ward, where sh was carefully monitored for signs of developin infection. Spontaneous premature labour was nc inhibited. If the patient developed signs of chori amnionitis, immediate delivery was undertaken otherwise, elective delivery was carried out at 32–3 weeks as a compromise between limiting the dura tion of uterine compression on the fetus, and nc exposing the neonate to the risks of extrem prematurity. During admission ultrasound examina tions were performed at weekly intervals (and mor often if indicated) to assess fetal growth, the volume of amniotic fluid, and fetal breathing movements. Oligohydramnios was defined as the absence of a pool of amniotic fluid greater than one centimetre in diameter in a vertical plane.[8] Fetal breathing was said to be present if a continuous period of chest wall movement persisted for longer than 60 seconds in any 30 minute period, with a breath to breath interval of less than six seconds.[9] [10] All ultrasound examinations were carried out within two hours of the patient receiving a concentrated dose of glucose.

After delivery the infants were carefully examined. The presence of physical deformities associated with the oligohydramnios tetrad were noted.[11] Pulmonary hypoplasia was diagnosed if the infant required high peak inspiratory pressures (in excess of 30 cm H_2O) during positive pressure ventilation both at resuscitation and subsequently, and if respiratory support was necessary for longer than one month.[6] Additional evidence was given by a chest radiograph (reported without clinical details) that was compatible with lungs of small volume. Necropsy was requested in the event of fetal or neonatal death. Pulmonary hypoplasia was confirmed if the lung:body weight ratio was less than 0:012 and the radial alveolar count less than or equal to 4·1.[12]

The infants were divided into three groups for analysis: group 1 comprised neonates with clinical or pathological evidence of pulmonary hypoplasia or both, group 2 comprised neonates with compressive limb abnormalities but no evidence of pulmonary hypoplasia, and group 3 comprised neonates with neither pulmonary hypoplasia nor limb abnormalities.

The significance of differences between the groups in the duration of rupture of the membranes and gestational age at its onset and at delivery were calculated by the Wilcoxon rank sum test.

Permission for this study was granted by the King's College Hospital ethics committee.

Results

During the year 30 patients were eligible for entry into the study. All chose to be managed expectantly and were therefore included. The pregnancies were all singletons without other complications. The mean gestational age at rupture of the membranes was 21·3 weeks (range 15–28).

Infection occurred in only two cases; both neonates were from group 3. In the first case although amniocentesis had shown white cells but no organisms, the infant died from infection in the first 48 hours of life after delivery by emergency caesarean section. The mother made a good recovery and had no evidence of postnatal infection. In the second case delivery by emergency caesarean section was undertaken at 28 weeks' gestation for placenta praevia. Although infection was not suspected antenatally the infant died early in the neonatal period from overwhelming sepsis. There were no other cases of maternal or neonatal infection.

Most of the patients delivered after the onset of spontaneous labour, 10 by the vertex and eight by assisted breech delivery. Six patients were delivered by emergency caesarean section; in four cases this was for fetal distress after the onset of spontaneous labour. One infant was born vaginally after induction of labour, and the remaining five babies were delivered by elective caesarean section between 32 and 34 weeks' gestation.

Eleven neonates died, an overall mortality of 36%, and in eight cases death was attributable to pulmonary hypoplasia. Of the 30 infants, 14 (46%) had physical deformities associated with oligo-

Table *Mean (range) gestational ages at onset of rupture of membranes and at delivery, and duration of rupture*

	Onset (weeks)	*Delivery (weeks)*	*Duration (weeks)*
Group 1	17 (15–22)	27 (24–34)	10 (4–19)
Group 2	18 (17–23)	31 (28–35)	13 (7–15)
Group 3	24 (18–28)	29 (25–35)	5 (2–10)

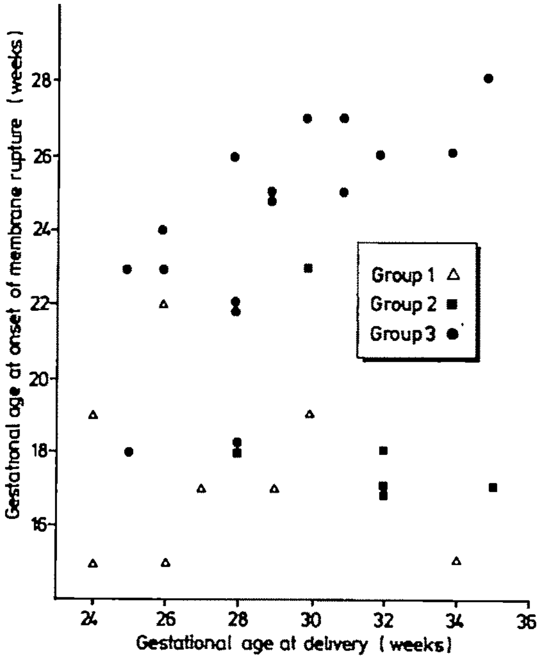

Figure *Gestational ages at onset of rupture of the membranes and delivery in the three groups* hydramnios[11] but no survivor had limb abnormalities that required surgical correction.

The mean gestational ages at rupture of the membranes and delivery in the three groups are shown in the table and the figure. The gestational age of the onset of rupture of the membranes was significantly earlier in groups 1 and 2 than in group 3 ($p<0{\cdot}01$). The duration of rupture of the membranes was only significantly longer when group 2 was compared with group 3 ($p<0{\cdot}01$). Infants in group 2 were delivered at a later gestational age than those in group 1 ($p<0{\cdot}05$), but there were no other significant differences in the timing of delivery among the three groups. All 30 pregnancies had similar degrees of oligohydramnios, but only in group 1 were fetal breathing movements never seen on ultrasound examination ($p<0{\cdot}01$).

GROUP 1

Eight infants had clinical evidence of pulmonary hypoplasia. Despite high peak inspiratory pressures (mean 38, range 30–55 cm H_2O), satisfactory oxygenation was never achieved, and all eight infants died within 48 hours of birth. Confirmation of pulmonary hypoplasia was obtained at necropsy in seven cases. The request for necropsy was refused by the parents of the other child. This infant required a maximum peak inspiratory pressure of 55 cm H_2O during artificial ventilation, developed bilateral pneumothoraces, and died at 24 hours of age; satisfactory oxygenation was never achieved All eight infants had Potter's facies and fixed flexion deformities.

GROUP 2

Six infants were born with compressive limb abnormalities without clinical evidence of pulmonary hypoplasia. Three of them did develop the respiratory distress syndrome and required ventilatory support, but none required peak inspiratory pressures in excess of 30 cm H_2O. The remaining three infants required no respiratory support in the neonatal period. The six infants had bilateral talipes, and three had mild Potter's facies, but none had congenital dislocation of the hips. All limb abnormalities responded to physiotherapy, and none required surgical correction.

GROUP 3

Sixteen infants had no abnormalities attributable to oligohydramnios. Although 11 infants required artificial ventilation for respiratory distress syndrome, the maximum peak inspiratory pressure used was less than 30 cm H_2O (mean 18, range 12–25 cm H_2O). Only one infant required prolonged ventilation. She was born at 25 weeks' gestation and developed severe respiratory distress syndrome, and a patent ductus arteriosus that required surgical ligation. Three of the 16 infants died, all three having been delivered before 34 weeks' gestation. At necropsy there was no evidence of pulmonary hypoplasia. One had delivered after the spontaneous onset of labour at 26 weeks' gestation and died of respiratory distress syndrome. The other two infants died of sepsis.

Discussion

Fatal pulmonary hypoplasia following premature rupture of the membranes is common, occurring in 26% of cases in this series and in 33%[5] and 21%[2] in two other studies. The gestational age at the time of rupture of the membranes was significantly associated with the development of pulmonary hypoplasia, and confirmed earlier findings that pulmonary hypoplasia was more common when rupture of the membranes occurred before 26 weeks' gestation.[2 13] Critical lung development occurs before 26 weeks' gestation,[14] and so damage after this time would be expected to have less effect on pulmonary growth and function. In 23% of neonates born without pulmonary hypoplasia, however, rupture of the membranes had occurred before 20 weeks' gestation.

There are several possible explanations for the association between pulmonary hypoplasia and oligohydramnios. Intrathoracic compression of the developing fetal lung, as associated with congenital diaphragmatic hernia and pleural effusions, often results in pulmonary hypoplasia.[15 16] It may therefore be that extra thoracic compression of the fetal chest by the uterine wall in the absence of the usual amniotic fluid cushion could have prevented normal lung growth. In this series, however, all pregnancies had the same degree of oligohydramnios (assessed by ultrasound examination) but only a proportion of the fetuses developed pulmonary hypoplasia. Ultrasound assessment of the volume of amniotic fluid is comparatively inaccurate, and it may be that minor differences in the volume of amniotic fluid that were undetectable by ultrasonography were responsible for the variation in outcome

Fetal breathing movements have been shown to be critical for normal lung growth.[17] In this series the absence of sustained respiratory activity was associated with the development of pulmonary hypoplasia. Though this seems contrary to findings reported recently,[18 19] this discrepancy is explained by the different definitions of fetal breathing movements used in the three studies. In the present series we considered fetuses to be breathing only if an episode of chest wall movement was continuous for at least 60 seconds with no breath to breath interval of greater than six seconds; this definition has been used extensively.[8 9 10 20] The other two studies[18 19] accepted fetuses to be breathing if respiratory activity persisted for only six seconds. We felt that that definition was unacceptable, because short bursts of fetal breathing movements or gasping can occur in severely hypoxic infants,[21 22] and thus cannot be used as an indicator of fetal well being. Indeed, in our series, such 'gasping' respiration was witnessed in fetuses who subsequently died of pulmonary hypoplasia.

Though the neonates that died of pulmonary hypoplasia had undergone earlier rupture of the membranes, other neonates with similar early onsets of rupture of the membranes had apparently normal lung development. Thus the gestational age at onset of rupture cannot be the sole explanation for the development of pulmonary hypoplasia. The length of time after the membranes had ruptured did not appear to be critical for the development of pulmonary hypoplasia as this was longer among the infants who had normal lung growth (group 2). Neither can the timing of delivery be incriminated, because there was no significant difference in the gestational age at delivery between infants in groups 1 and 3. Our results suggest, therefore, that the development of pulmonary hypoplasia in pregnancies with early rupture of the membranes is associated with the disappearance of fetal breathing movements. Sustained periods of fetal breathing seem to preserve lung growth even when rupture occurs within the 'critical' period of lung growth.

Pulmonary hypoplasia after oligohydramnios can occur in isolation without limb abnormalities.[23 24] In this series, however, there were infants with flexion deformities of the limbs with normal lung growth, which is unusual.[4 25] The limb abnormalities were significantly associated with both the time of onset and the duration of oligohydramnios. Fetal immobilisation in utero as a consequence of paralysing drugs given to the mother, or musculoskeletal disorders of the fetus, result in fixed flexion deformities.[26] It is likely that the association between oligohydramnios and fixed flexion deformities is caused by prolonged compression by the uterus resulting in fetal immobilisation. This hypothesis is supported by the finding of a significantly longer duration of oligohydramnios and later gestation at delivery in this group of infants. In our series none of the surviving infants required more than passive physiotherapy to correct the limb abnormalities. In all cases delivery occurred before 35 weeks' gestation, and it may be that this prevented progression of the limb abnormalities.

Infection has been proposed as a cause of premature rupture of the membranes[27] and as a consequence there has been concern that expectant management of such pregnancies might lead to serious maternal complications.[1] In this series we excluded all pregnancies with rupture of the membranes of less than two weeks' duration. This may have prevented us including pregnancies for expectant management who had rupture as a result of intrauterine infection. This series has shown that long standing rupture of the membranes is not often associated with infection. We had only one case where infection was suspected antenatally, and this was not confirmed in the mother though the neonate died of sepsis. One other infant died early in the neonatal period of sepsis; the mother never exhibited signs of infection either in the antenatal or postnatal period.

Premature rupture of the membranes before 20 weeks' gestation poses a difficult problem in management. A large proportion of such pregnancies will either abort spontaneously, or develop infection shortly after rupture of the membranes necessitating termination of the pregnancy In the present study we included only pregnancies in which rupture of the membranes had lasted for at least two weeks' gestation; thus epidemiological statements about the outcome of all pregnancies with rupture of the membranes before 20 weeks' gestation cannot be made. It is interesting to note, however, that among our patients with rupture of the membranes before 20 weeks' gestation, none developed sepsis and though 50% died from pulmonary hypoplasia the others survived intact or with minor orthopaedic problems.

The results of this study show that premature and prolonged rupture of the membranes can be associated with intact neonatal survival, although the mortality of 26% and morbidity of 27% is considerable. The presence of fetal breathing movements, even in pregnancies with rupture of the membranes at as early as 18 weeeks' gestation was associated with normal lung growth and favourable outcome in all cases. Our results suggest that in such pregnancies expectant management is a reasonable course, but that delivery should be instituted electively before full term to reduce the possible morbidity caused by limb abnormalities.

Dr M Blott, research fellow, is supported by Action Research for the Crippled Child.

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Accepted 27 June 1988

Archives of Disease in Childhood, 1988, **63,** 1151–1167

Personal paper

Retinopathy of prematurity: clinical implications of retinal development

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Retinopathy of prematurity (ROP) is a potentially blinding ocular disorder that is unique to the preterm infant. The current epidemic affects the smallest and illest preterm survivors of modern neonatal intensive care units. With the prevention of neonatal asphyxia, judicious curtailment of oxygen, and adequate doses of vitamin E, ROP has become a disorder that is generally restricted to infants weighing less than 1001 g at birth. The size of the surviving population of infants with ROP dwarfs all previous predictions of absolute numbers because survival rates of infants weighing 501–750 g at birth are now approaching 60%, and those of infants weighing 751–1000 g are now approaching 90%.

The total incidence of ROP in infants weighing 501–750 g is almost 100% with severe ROP developing in about 30%. The total incidence of ROP in infants weighing 751–1000 g is almost 80% with severe ROP developing in about 10%. Whether the future total incidence of ROP and that of severe ROP will change is dependent on the unknown effects of the many new developments in the care of premature infants.

NORMAL RETINAL DEVELOPMENT

The immature retina has two blood supplies, the choroidal vessels and the inner retinal vessels (fig 1). The choroidal vasculature develops early, lies on the

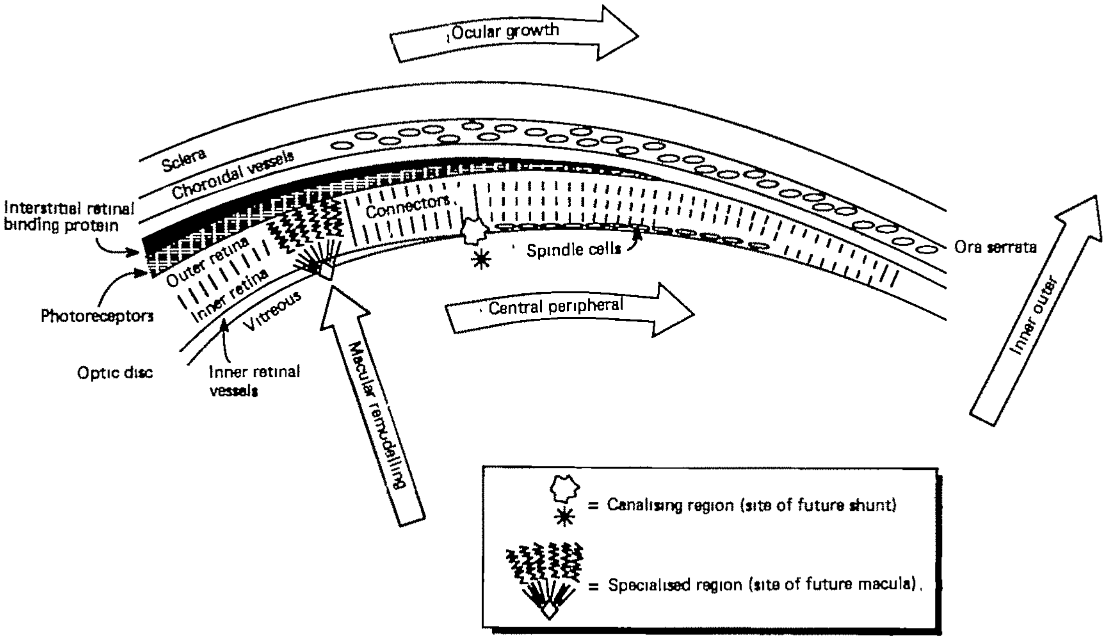


Fig 1 *Four interrelated and concomitant processes (arrows) that regulate normal retinal development. Note thinning of retina towards ora serrata, region of future shunt where ROP is first seen clinically, and region of future macula that will determine ultimate visual acuity*

outer surface of the retina, and is the sole supplier of nourishment to the thin, undifferentiated retina. The inner retinal vasculature develops late, lies within the inner surface of the retina, and nourishes the inner portions of the thick, maturing retina. This inner retinal vasculature develops from a peripheral migration of spindle cells from the optic disc. In utero, spindle cells in the thin, peripheral, avascular retina reside in a comparatively hypoxic environment.

PATHOLOGICAL EVENTS OF NEOVASCULARISATION AND TRACTION

After premature birth, spindle cells in the thin, peripheral, avascular retina are stressed by a comparatively hyperoxic environment. This stimulus for abnormal retinal development occurs because oxygen diffuses freely across the retina from the choroidal vasculature that cannot vasoconstrict. Spindle cells stressed by free radical damage stop migrating peripherally, stop forming inner retinal vessels by the process of canalisation, and begin to synthesise and secrete angiogenic factors For about eight to 10 weeks these angiogenic factors induce abnormal inner retinal neovascularisation at the boundary between the vascular and avascular retina (fig 1). This boundary becomes a shunt that contains a large volume of rapidly flowing blood.[1–4] After this two month period myofibroblasts begin to differentiate from a stem cell line in the shunt, they form contractile sheets that invade the vitreous for about four months, and they may cause traction leading to retinal detachment.[1 3–4] This entire cascade of events can be interrupted and regress spontaneously, or can continue to progress relentlessly. In either case, the overall enlargement of the eye continues. This pathogenesis is different from other neovascularisations of the mature eye, such as those associated with diabetes and sickle cell disease.

Retinal development

There are four interrelated and concomitant processes that are important to an understanding of ROP (fig 1). These consist of a central/peripheral vector of retinal development that is coupled simultaneously with an inner/outer vector of retinal differentiation, a remodelling of the macular region, and overall ocular growth.

CENTRAL/PERIPHERAL AND INNER/OUTER VECTORS

Retinal development into the outer retina, connectors, and inner retina begins centrally at the optic disc and advances peripherally to the ora serrata. With respect to ROP there are two important central/peripheral developmental processes: photoreceptors in the outer retina and spindle cells in the inner retina (fig 1).

Photoreceptors begin to differentiate from the outer neuroblastic retina and advance as a gradient of maturation (figs 1 and 2). There are at least two stimuli for the normal formation of inner retinal vessels. One stimulus is the thickening of the maturing retina that displaces the inner retina further and further from the choroidal vessels. Another stimulus is that as photoreceptors mature their metabolic rate increases, and they utilise more and more oxygen that diffuses from the nonvasoconstricting choroidal vasculature. Maturing photoreceptors secrete interstitial retinol binding protein into the space between the retinal pigment epithelium and the neural retina. This protein appears round the optic disc as early as 20 weeks' gestation and reaches the ora serrata at 29 weeks' gestation (a total transit time of nine weeks).[5] Its presence in the subretinal space is critical to the potential retinal uptake of fat soluble vitamin E, and its extent establishes the area of retina that can be protected by vitamin E.[6] After premature birth oxygen can diffuse easily from the non-vasoconstricting choroidal vasculature, can cause physiological vasoconstriction of the inner retinal vasculature (but not endothelial necrosis and retraction), and can create an abnormal hyperoxic environment for spindle cells. Interstitial retinol binding protein carries vitamin E (only in the preterm infant) into the connectors (Muller cells), and the connectors carry vitamin E across the retina to spindle cells.

Spindle cells migrate in the inner retina from the optic disc to the ora serrata (figs 1 and 2). Spindle cells appear round the optic disc at 16 weeks' gestation and reach the ora serrata at 29 weeks' gestation (a total transit time of 13 weeks). After 29 weeks' gestation the spindle cell apron continually decreases in its linear extent so that the spindle cell apron has completely disappeared and the inner retinal vasculature is completely formed at 40 weeks' gestation. In the smallest infants the proximal portion of the spindle cell apron is intermingled with the formed vessels, and a few spindle cells may even remain in the adventitia of the hyaloid artery at the optic disc; in larger infants the spindle cell apron is not intermingled with the formed vessels, and spindle cells do not remain at the optic disc. A small region of the spindle cell apron anterior to the last formed vessels continues the inner retinal vasculature by canalisation.

The transretinal geometry between the slowly migrating spindle cells (13 weeks transit time) and the faster developing photoreceptors (nine weeks transit time) that are secreting interstitial retinol binding protein changes with gestational age.[7] In

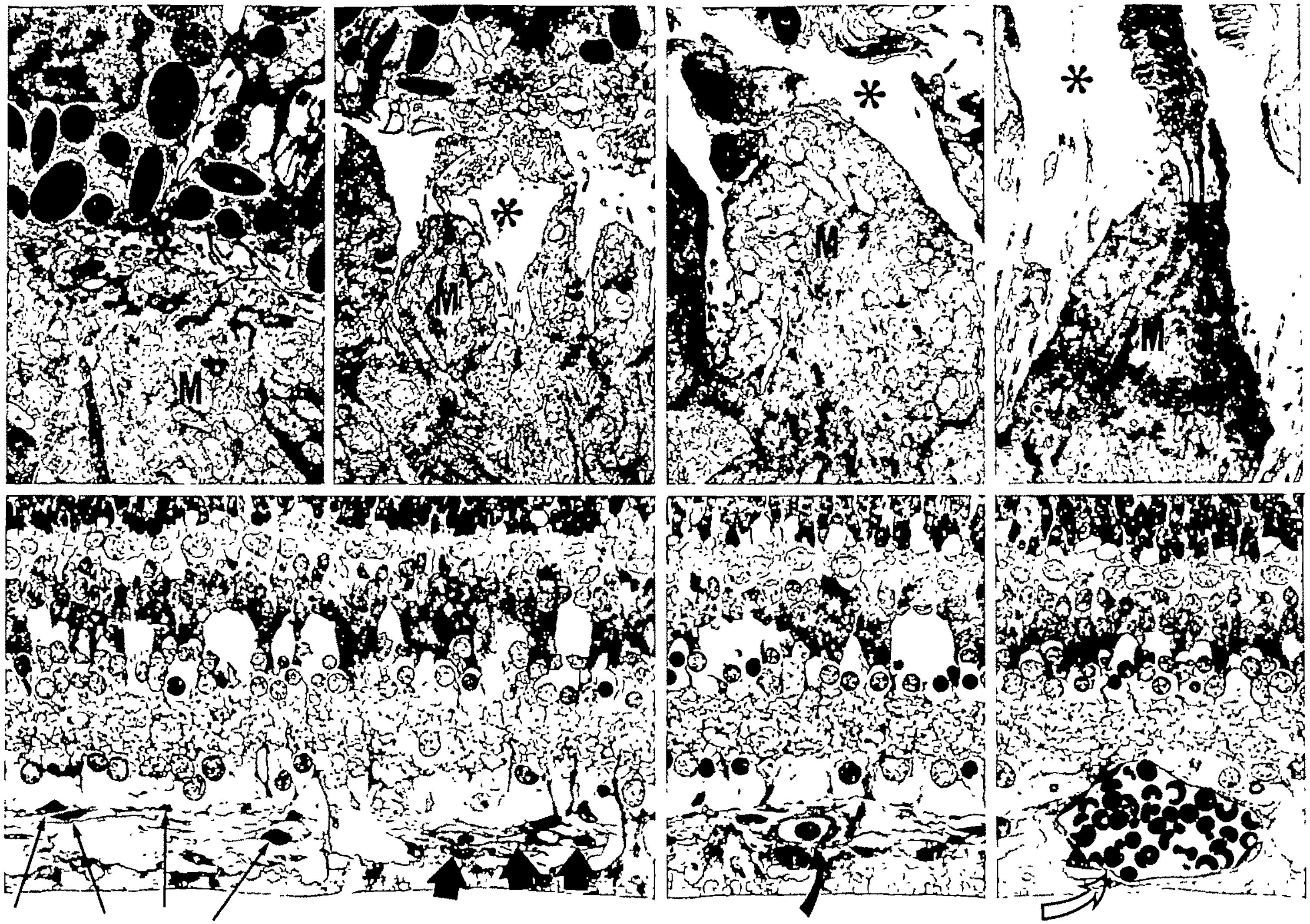


Fig 2 Gradient of maturing photoreceptors in outer retina (top left to right) is associated with inner retina (bottom left to right) with migrating spindle cells (arrow), canalising spindle cells (arrow head), capillaries (curved arrow), and mature vessels (open arrow) Top transmission electron micrographs (magnification of 11 000). Note increasing mitochondria (M) in photoreceptors and increasing space (asterisk) between the retinal pigment epithelium and the neural retina Bottom light micrographs (magnification of 320)

infants weighing less than 1001 g at birth (27 weeks' gestation or less), most of the spindle cell apron is transretinal to photoreceptors that are not secreting interstitial retinol binding protein, and therefore these spindle cells are less likely to receive adequate protection from vitamin E. Thus even if vitamin E is given and oxygen is judiciously curtailed ROP may still be severe in the iller infants weighing less than 1001 g at birth. This morphological fact explains the clinical reality that vitamin E supplementation to eliminate plasma deficiency, even supplementation to pharmacological plasma concentrations, cannot protect all surviving infants from ROP.

In infants weighing 1001–1500 g at birth (28–32 weeks' gestation) most of the spindle cell apron is transretinal to photoreceptors that are secreting interstitial retinol binding protein, and therefore these spindle cells can receive adequate protection from vitamin E. Thus if vitamin E is given and oxygen is judiciously curtailed, ROP is usually not severe in these infants. Without vitamin E, however, ROP may be severe in the illest of the infants weighing 1001–1500 g at birth. Thus in analysing the results of trials of vitamin E for protection against ROP, a multivariate analysis with birth weight as one variable must be used rather than a univariate analysis. In infants weighing more than 1500 g at birth (more than 32 weeks' gestation), fewer and fewer spindle cells remain within the retina. Thus whether or not vitamin E is given, but if oxygen is judiciously curtailed, severe ROP does not usually develop.

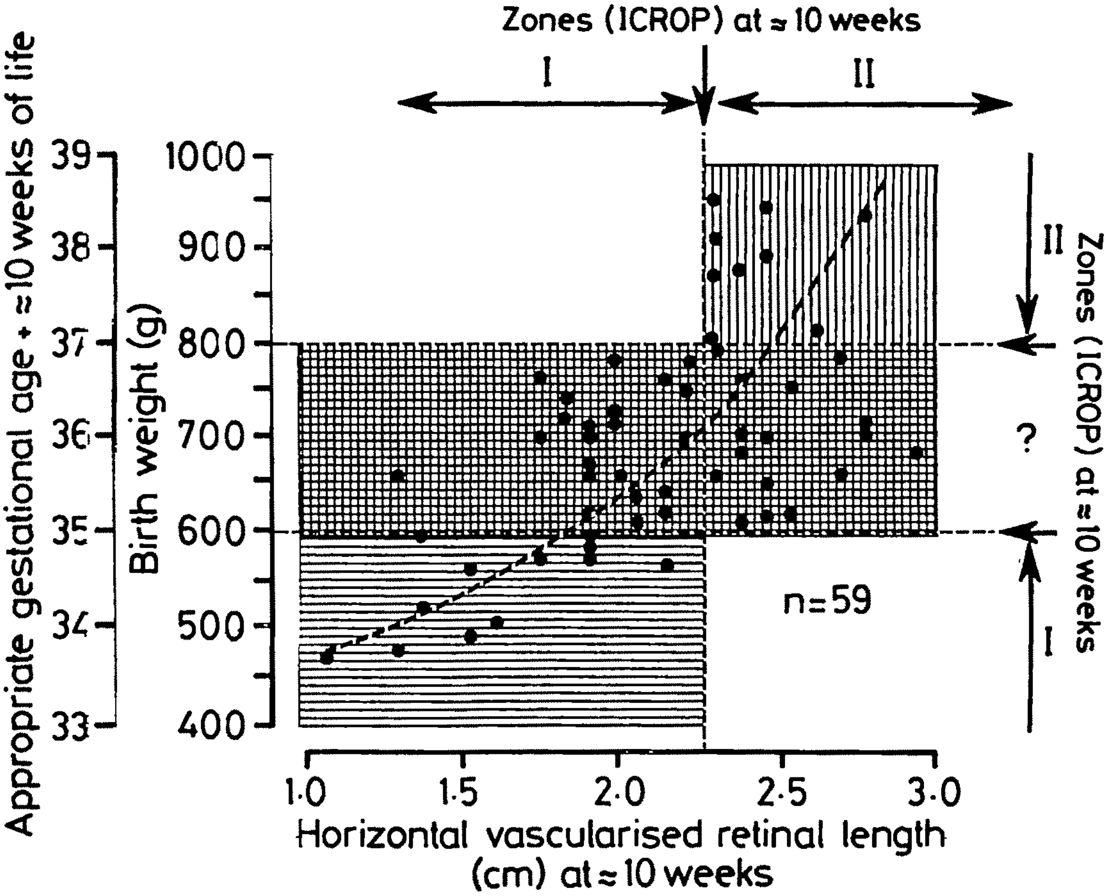


Fig 3 *Extent of the vascularised retina (horizontal vascularised retinal length (cm) at about 10 weeks) and zones (international classification of ROP at about 10 weeks of age) is associated with birth weight (g), appropriate gestational age+about 10 weeks of life, and zones at about 10 weeks of age Horizontal lines denote area of obligate zone I ROP Vertical lines denote area of obligate zone II ROP. Combined horizontal and vertical lines denote area of zone I or II ROP (area of biological variability)*

The extent of inner retinal vascularisation is directly associated with gestational age and birth weight (fig 3). The clinical importance of this association is that if severe ROP develops eight to 10 weeks after birth in infants appropriate for gestational age, those weighing 600 g or less will have ROP in zone I and those weighing 801 g or more will have ROP in zone II. Those infants weighing 601–800 g may have ROP in either zone I or zone II.[8] This reflects the normal biological variability seen in all developmental processes. Thus the inner retinal vasculature establishes the area of retina that equates to the zones in the international classification of ROP,[9 10] that does not secrete angiogenic factors,[4] and that may be rescued by cryotherapy to the peripheral retina where the spindle cells reside. Cryotherapy entails placing a cold probe on the external surface of the eye to destroy all the living cells between the external surface and the vitreous. Retinal development along the central/peripheral vector stops after cryotherapy, but further retinal development associated with the inner/outer vector continues.

MACULAR REMODELLING

The macula is a specialised region of the posterior retina that is responsible for all fine visual acuity (fig 1). It is an avascular region in which the inner retina is displaced circumferentially 360° so that light can impinge perpendicularly on the perfectly parallel discs of the cone photoreceptors. The commitment to macular development and its subsequent remodelling must be triggered by an interplay between the inner/outer vector. This region is incompletely developed until three months after birth in an infant born at full term. Clinically the macula appears immature before this time—that is, it does not have a dimpled appearance.

The distance between the temporal rim of the optic disc and the centre of the macula is constant in all normally developing or developed human eyes. With the development of severe ROP the distance between the temporal rim of the optic disc and the centre of the macula may be increased by dragging, whether the ROP regresses spontaneously or is treated successfully by cryotherapy.

OCULAR GROWTH

As the retina develops along the central/peripheral and inner/outer vectors with macular remodelling, the overall diameter of the globe increases rapidly with only 15% of the increase in the diameter of the globe occurring after 40 weeks' gestation (figs 1 and 4). Unless phthisis (ocular death with shrinkage) occurs, the globe continues to enlarge after the development of severe ROP, with or without surgical intervention. Whether ROP is regressing or progressing, this concept of ocular growth is important when retinal detachment caused by severe traction (from substantial invasion by myofibroblasts) occurs.

Neovascularisation (spindle cells)

INITIATION

After preterm birth normally migrating and canalising spindle cells can become stressed by free radicals The probability that this stress to spindle cells stimulates the development of severe ROP is greatest in the smallest and illest preterm infants. The stress is seen ultrastructurally as early as the fourth day of life as a formation of extensive gap junctions between adjacent spindle cells uniformly throughout the apron (fig 5a, 5c). Shortly afterwards these gap junction linked spindle cells contain an extensive volume of rough endoplasmic reticulum (fig 5b, 5d). This indicates increased communication between cells (gap junctions), and increased protein synthesis and secretion (rough endoplasmic reticulum). Increased amounts of angiogenic factors have been detected only from homogenates of the peripheral retina when gap junction linked spindle cells are present.[4 7] This state exists for about eight to 10 weeks.[1–4]

After eight to 10 weeks of synthesis and secretion of angiogenic factors, extensive gap junctions between adjacent spindle cells disappear uniformly throughout the apron, the extensive volume of rough endoplasmic reticulum decreases, and all spindle cells stack within the inner retina. The stimulus for the stacking of the spindle cells is unknown; this subclinical event indicates, however, that peripheral spindle cells are no longer the stimulus for neovascularisation and that severe ROP will either regress or progress for unknown reasons.[1–4]

KINETICS

At all gestational ages the moment of premature birth usually initiates the development of ROP. The development may, however, be initiated before birth by an intrauterine catastrophy, in which case the disease may be seen earlier than eight to 10 weeks after birth. Similarly, the initiating event may occur weeks after premature birth if the oxidant/antioxidant balance is upset before completion of the inner retinal vasoformation with disappearance of all spindle cells, in which case the disease may be seen eight to 10 weeks after the delayed imbalance. Development of severe ROP is a predictable cascade of events triggered by stressed spindle cells and their subsequent synthesis and secretion of angiogenic factors for a given length of time.

Conceptional age (gestational age at birth plus weeks of life) should not be applied to the timing of the development of severe ROP or to the timing of surgical intervention. Conceptional age, however, may be applied to the concept of a given posterior area of vascularised inner retina (ROP stage 3+) that can be dragged by an actively contractile sheet of myofibroblasts, by a fixed inactive remnant

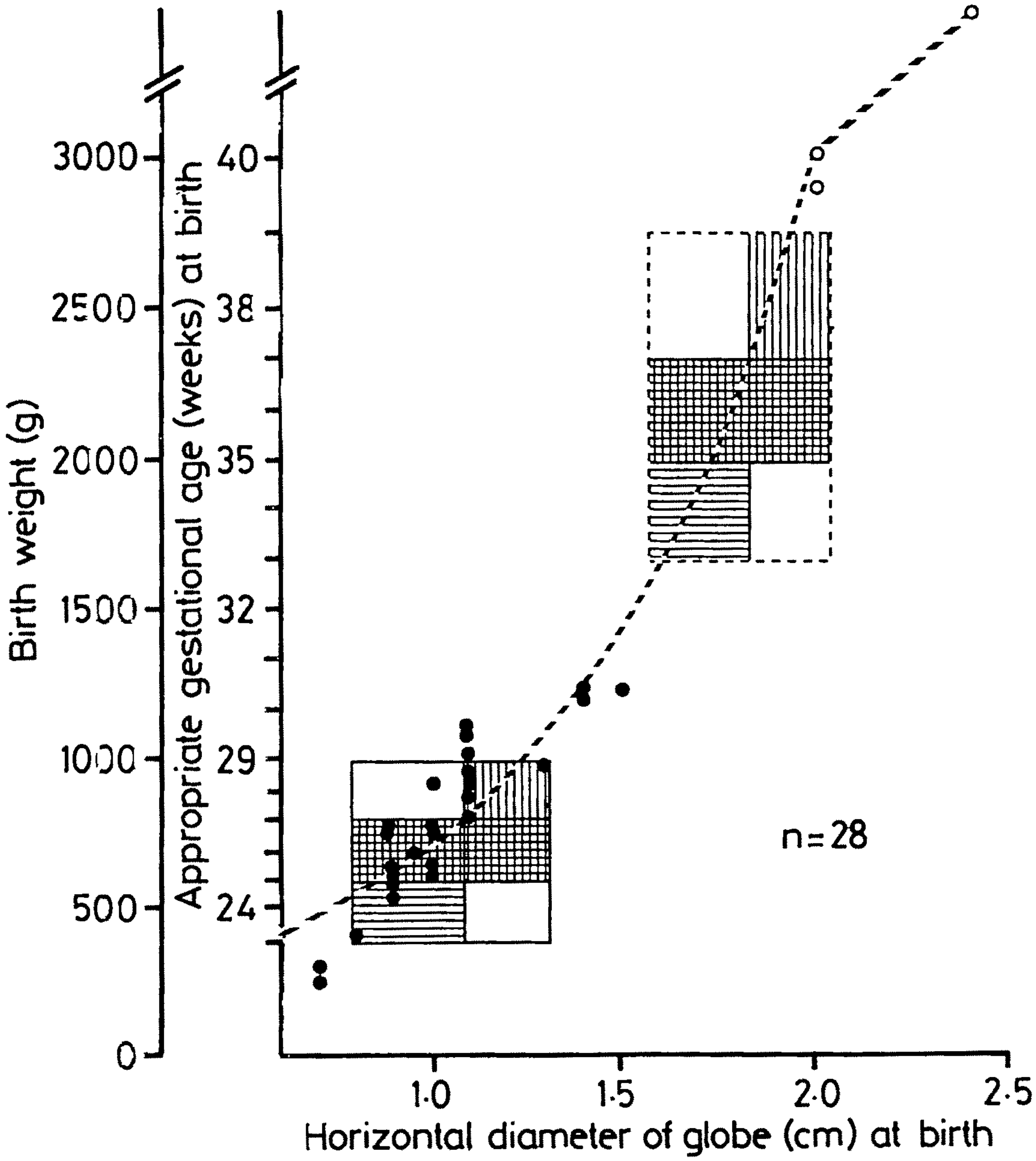


Fig 4 Size of eyes (horizontal diameter of globe (cm) at birth) is associated with birth weight (g) and appropriate gestational age (weeks) at birth. The solid box indicates ocular size at birth. The dashed box indicates the predicted ocular size 10 weeks after birth. The horizontal lines, vertical lines, and combined horizontal/vertical lines are the same as in fig 3 Closed circles are preterm infants Open circles are term infants and adults The eyes with zone I ROP treated at about 10 weeks have more growth yet to occur than similar eyes with zone II ROP.

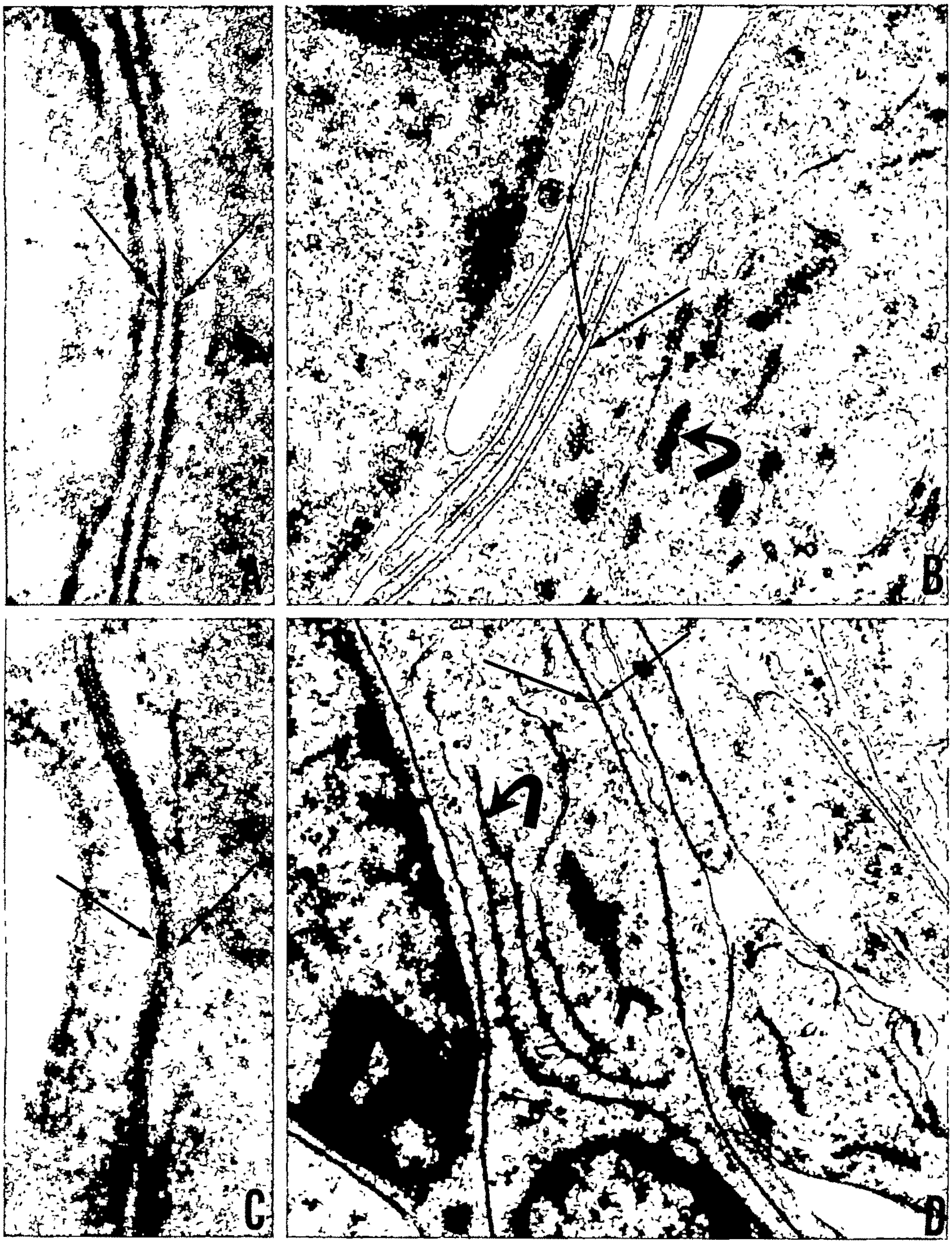


Fig 5 *Migrating spindle cells (A and B) have adjacent plasma membranes (arrows) with no gap junctions and minimal rough endoplasmic reticulum (curved arrows). In contrast, stressed spindle cells (C and D) have adjacent plasma membranes (arrows) with gap junctions and moderate rough endoplasmic reticulum (curved arrows). Transmission electron micrographs: A and C magnification of 140 000, B and D magnification of 32 000*

Table 1 *Risk factors for retinopathy of prematurity*

Clinical fact	*Clinical event*	*Effect on spindle cells*
Immaturity:		
Increased survival of infants weighing <1000 g	Low birth weight, low gestational age, surfactant	The smaller the infant, the larger the area of spindle cells in the inner retina with insufficient interstitial retinol binding protein in the outer retina
Free radical damage:		
Acidosis	Acute hypothermia, acute hypoxia, chronic hypotension (dopamine)	Subsequent reperfusion of retinal tissue results in increased oxygen consumption
Large amounts of oxygen given	Better ventilation, pneumothorax, bronchopulmonary dysplasia, patent ductus arteriosus, apnoea	More oxygen free radicals trigger increased formation of gap junctions between spindle cells
Increased amount of oxygen released to tissues by adult haemoglobin	Transfusion of blood for intraventricular haemorrhage, hyperbilirubinaemia, clinical laboratory monitoring	Replacement of fetal haemoglobin by adult haemoglobin shifts the dissociation curve so that more oxygen is released to the retina through the choroidal vessels
Microbiologically confirmed sepsis	Bacterial, fungal, viral systemic infections	Ingestion of pathogens by macrophages leads to the release of oxygen free radicals by macrophages
High light intensity	Unusually high, continuous light in the modern neonatal intensive care unit	Continuous, high light damages the developing photoreceptors so that they consume less of the oxygen that is arriving through the choroidal vessels and more oxygen reaches the spindle cells

Table 2 *Comparison of four randomised masked controlled clinical trials that evaluated the effect of prophylaxis with vitamin E on the suppression of development of severe ROP*

	Hittner et al[12]	*Finer et al*[13]	*Johnson et al*[14]	*Phelps et al*[15]
Study design:				
When study was conducted	November 1979 to December 1980	July 1978 to April 1981	January 1979 to May 1981	December 1980 to August 1983
Year that results were published	1981	1982	1988	1987
Initial route of administration	Oral	Intramuscular	Slow intravenous infusion, or intramuscular	Rapid intravenous infusion
Form of vitamin E used	Alcohol	Acetate	Alcohol	Alcohol
Mean vitamin E level in study (mg%)	1·2	4·6	5·0	3·5
Infants studied (all weighed <1500 g at birth)—control/treatment groups:				
Mean birth weight (g)	1050/1050	1203/1185	1156/1162	1205/1181
No receiving first dose of vitamin E within 24 hours of birth	75/75	64/62	194/186	147/140
No of infants whose eyes were examined when they were >8 weeks of age	51/50	50/47	147/141	99/97
No of infants that died	24/24	14/15	47/45	29/31
No of infants excluded	0/1	0/0	0/0	19/12
Toxic effects reported	None	None	Necrotising enterocolitis, sepsis	Intraventricular haemorrhage, retinal haemorrhages
Outcome of ROP—control/treatment groups				
ROP $\geq$stage 3+, weighing $\leq$1500 g at birth	5/0	3/0	7/3	1/1
ROP $\geq$stage 3+, weighing $\leq$1000 g at birth	4/0	2/0	5/3	1/1
p Value	0·01	0·01	0·05	NS

myofibroblast ridge, or by ocular growth not accompanied by further retinal development, along the central/peripheral vector. Thus loss of retinal function by dragging without detachment, or by retinal detachment, is an event that is often delayed by months or years and is associated with continuous traction for some time.

RISK FACTORS

The risk factors of ROP are those clinical events that stress spindle cells. These events fall into two groups: immaturity and free radical damage (table 1).[1–4] Additionally, maternal angiogenic factors caused by diabetes or hyperthyroidism may initiate the development of severe ROP that follows a time sequence indicating an intrauterine onset. A combination of genetic factors may also induce a clinical appearance that mimics severe ROP but which is histologically distinct.[11]

ANTIOXIDANT: VITAMIN E SUPPLEMENTATION

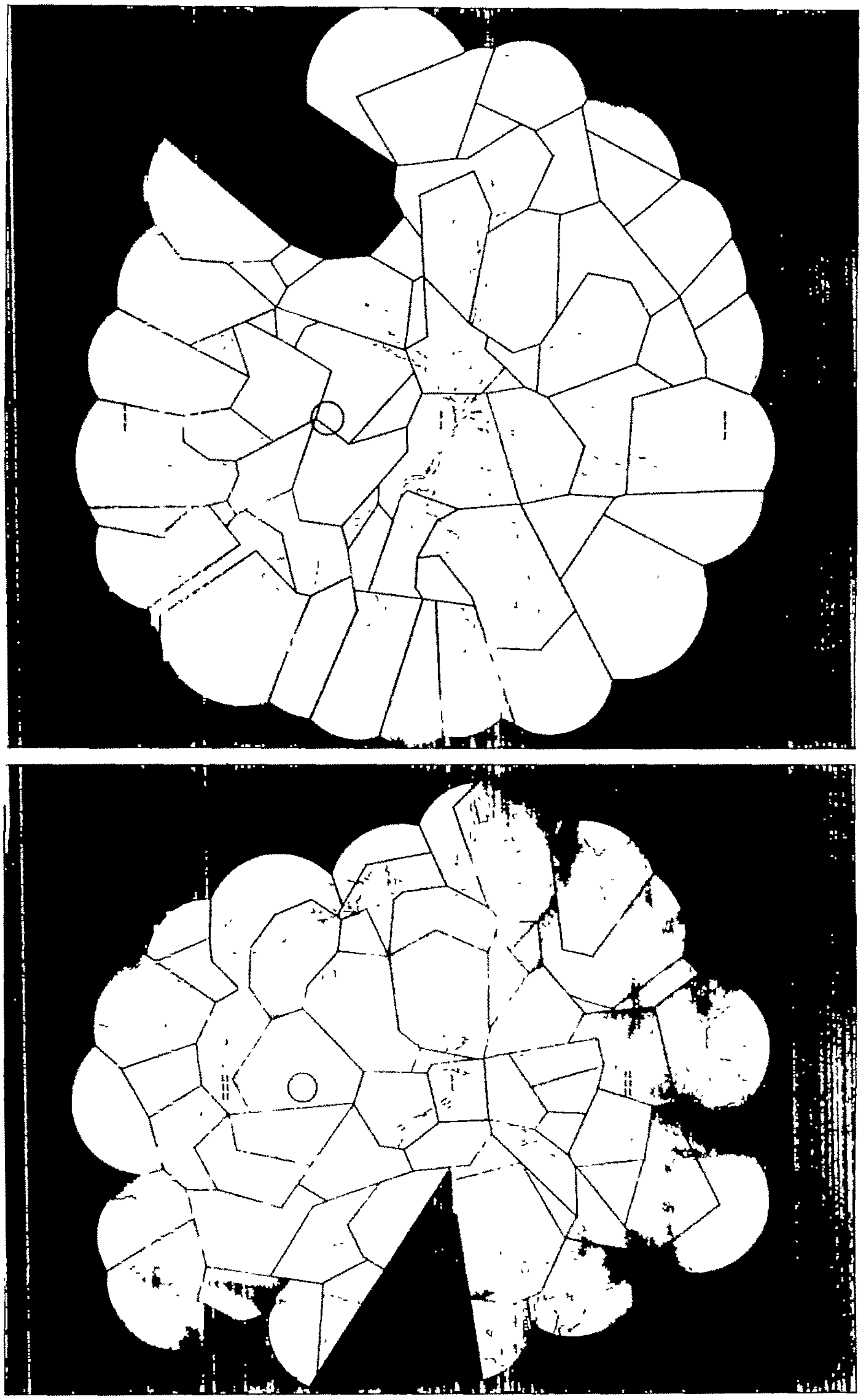
There have been four randomised, masked controlled clinical trials to evaluate the effect of prophylaxis with vitamin E on the suppression of the development of severe ROP (table 2).[12–15] The protocol for each trial was designed so that vitamin E should be given from the first day of life and should be continued without interruption until inner retinal vascularisation was complete. Each used different vitamin E preparations, achieved different plasma vitamin E concentrations, used a different initial route of administration, evaluated ROP by different classification systems, set different end points for analysis, and had different percentages of infants lost to follow up.

The three clinical trials in which prophylaxis with vitamin E was shown to be effective may be explained by the spindle cell/myofibroblast pathogenesis of ROP. Early and continuous vitamin E supplementation resulted in sufficient retinal uptake to stabilise spindle cell membranes against free radical damage in almost all infants weighing 1001–1500 g at birth. This supplementation also partially protected most extremely high risk infants (those weighing 1000 g or less at birth) unless several risk factors were present. Johnson *et al* in their initial report took one year as their end point, which allowed exclusion of a few totally blind infants in the control group who died before 1 year of age.[16]

The single trial in which prophylaxis with vitamin E was not shown to be effective[15] may also be explained by the spindle cell/myofibroblast pathogenesis of ROP. The initial, rapid intravenous infusion may have resulted in delayed uptake into the retina caused by sequestration by the liver of the transiently high plasma vitamin E concentrations. This may have left the spindle cells in an unfavourable oxidant/antioxidant balance for long enough to induce formation of gap junctions. Some of the treated infants received doses intended for infants in the control group in error; this interrupted the prophylaxis. Thus even if there was initial stabilisation of the spindle cell membranes, spindle cells may have been left in an unfavourable oxidant/antioxidant balance for long enough to induce formation of gap junctions. The incidence of intraventricular haemorrhage was increased in those infants receiving treatment. There is a close association between intraventricular haemorrhage and ROP; thus the incidence of ROP in the infants receiving treatment may have been artificially increased, which would have masked any effect of vitamin E on the suppression of the development of severe ROP. This increased incidence of intraventricular haemorrhage is not in accordance with the results of Speer *et al*[17] or Sinha *et al*,[18] and may have been caused by the initial rapid intravenous infusion. Vitamin E may have displaced vitamin K at its binding site.

The issue of vitamin E supplementation to suppress the development of severe ROP was recently reviewed by the Institute of Medicine of the National Academy of Sciences.[19] The committee concluded that there was no definite evidence of either benefit or harm from prophylaxis with vitamin E against ROP, and that the risks of giving vitamin E seem to be minimal for premature infants provided that the doses are kept low enough to achieve a blood concentration of no higher than 3 mg%.

Our personal clinical experience since 1979 with vitamin E prophylaxis is more favourable. No infant who weighed greater than 1001 g at birth, who received vitamin E according to our protocol, and who did not have severe hypoxia during delivery or severe hypotension with subsequent reperfusion, has developed severe ROP. Thus a sufficient retinal uptake of plasma vitamin E must be stabilising most of the spindle cell apron and halting the cascade of events that may ultimately result in traction and retinal detachment. The development of severe ROP in infants weighing 1000 g or less at birth is delayed. Insufficient retinal uptake of plasma vitamin E caused by there being insufficient amounts of interstitial retinol binding protein in the subretinal space may only transiently suppress formation of gap junctions between spindle cells in the inner retina. Thus in the smallest and illest infants, prophylaxis with vitamin E may ultimately fail to prevent sufficient spindle cell membrane damage. Severe ROP develops about two weeks later than in similar infants not receiving vitamin E.



The overall incidence of all stages of ROP is not decreasing because the protection given to plasma membranes by vitamin E is not an 'all or nothing' effect, and is by no means a panacea. Vitamin E prophylaxis is drastically decreasing the severity of ROP in infants weighing between 1001 and 1500 g at birth.

The ultimate clinical question is whether vitamin E prophylaxis to decrease the development of severe ROP can be justified for all infants weighing 1500 g or less at birth. The issue of its safety has been at the root of the controversy. With our protocol we have not seen a single case of toxicity from vitamin E prophylaxis in our centre since we began giving it in 1979. All reported toxic reactions[20] have resulted from high peaks of plasma vitamin E given by rapid intravenous administration (up to 15 mg%), or high, sustained plasma vitamin E concentrations achieved by slow intravenous infusion or intramuscular injection (more than 8 mg% for several days), or the high osmolality of oral vitamin E preparations (more than 2000 mOsm), or the use of improper carriers in small amounts to make intramuscular preparations soluble (sesame seed oil, Emulphor El–100, and polysorbate 80), or the use of toxic polysorbate carriers in large amounts in E-ferol. E-ferol is a drug that was illegally sold in the United States for a short time from late 1984 to early 1985; it was recalled after many deaths had been reported, for which civil and criminal actions were taken.

OUR CURRENT RECOMMENDATIONS CONCERNING VITAMIN E

To suppress the development of severe ROP, we give 100 mg/kg/day of *dl*-α-tocopherol (or *dl*-α-tocopheryl acetate) orally in a medium chain triglyceride solution from the first hours of life until retinal vascularisation is complete. To suppress the development of severe intraventricular haemorrhage,[17 18] we give 15 mg/kg intramuscularly or 5 mg/kg intravenously over eight hours as soon as possible after delivery, and 10 mg/kg intramuscularly or 3 mg/kg intravenously over eight hours on the second day of life. To maintain mean plasma vitamin E concentrations between 1·2 and 3·5 mg% until oral feedings can be started (or if oral feedings are interrupted) we give 10 mg/kg intramuscularly every third day or 3 mg/kg/day intravenously over eight hours. We use only *dl*-α-tocopherol in water.

ANTIOXIDANT: SELENIUM SUPPLEMENTATION

Because vitamin E provides incomplete, age dependent, antioxidant protection against the development of severe ROP, future research must focus on antioxidant systems that are already endogenous to the retina of the infant weighing 1000 g or less at birth and that can be stimulated by water soluble substances. Vitamin C is an antioxidant system that meets these criteria; the system is, however, already operating maximally in infants of all gestational ages.[6] Two independent laboratories have documented high retinal concentrations of selenium dependent glutathione peroxidase in all premature infants weighing 160 g or more at birth.[21 22] Perhaps selenium supplementation from the first hours of life will maintain the activity of this antioxidant system and protect spindle cells in all infants who are likely to survive.

Traction (myofibroblasts)

REGRESSION OF STAGES 1, 2, OR MILD STAGE 3 ROP

When regression of mild ROP (international classification of ROP stages 1, 2, or mild stage 3) occurs, synthesis and secretion of angiogenic factors stop, gap junctions between adjacent spindle cells disappear uniformly throughout the apron, the extensive volume of rough endoplasmic reticulum decreases, and spindle cells remain as an apron. When regression of mild ROP occurs, inner retinal vasoformation continues by canalisation and reaches the ora serrata. Peripheral and posterior retinal and vascular changes tabulated by international classification of ROP[10] do not follow stages 1 or 2 ROP, and there is no evidence of any remnants of myofibroblasts. These changes are minimal after mild stage 3 ROP, and there are minimal remnants of myofibroblasts, but usually no appreciable

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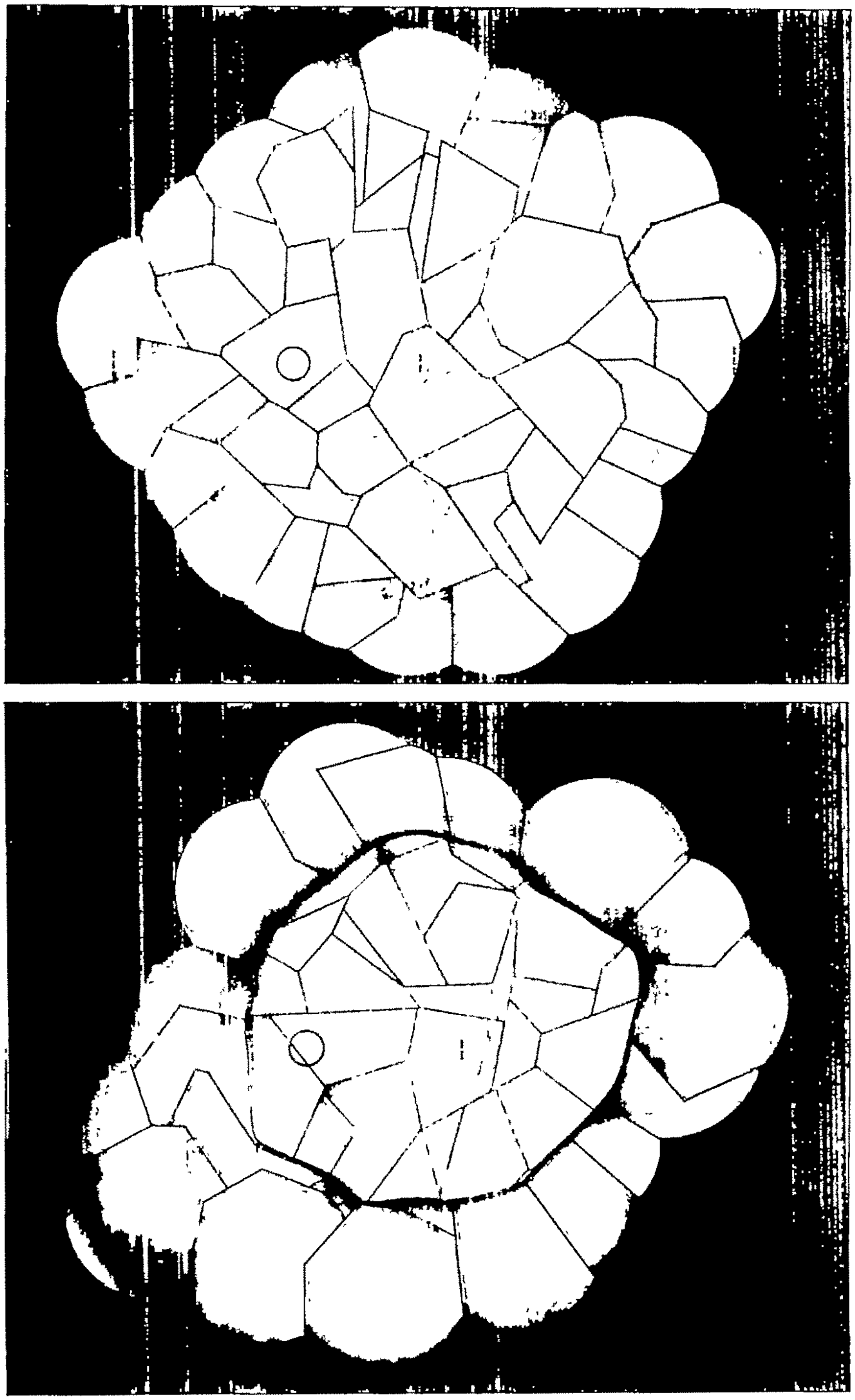
Fig 6 *Top. preoperative appearance at the age of 10 weeks of right retina of an infant weighing 650 g at birth with zone II stage 3+ ROP. Note the extent of vascularised retina (distance between the pair of three vertical dashes equals 2·5 cm of retina), and immature macula (circle); and the distance between the temporal rim of the optic disc (two vertical dashes) and the centre of the macula equals 0·5 cm of retina). Moderate plus disease and moderate invasion of myofibroblast are present. Bottom: postoperative appearance of the same eye at the age of 10 months Note extent of viable retina (distance between the pair of three double vertical dashes equals 1 9 cm of retina), temporally displaced macula (circle), and distance between the temporal rim of the optic disc (two vertical dashes) and centre of the macula equals 0 7 cm of retina. Dragging of posterior vessels and the region of full thickness cryotherapy are visible Fixation is unsteady (nystagmus) in this myopic (−9·00) eye at the age of 21 months. Comparison of these two retinal montages shows that cryotherapy to the avascular retina and shunt alone do not guarantee a favourable outcome with respect to macular function*



dragging of the larger retinal vessels, or of the macula.

REGRESSION OF SEVERE STAGE 3 ROP

When regression of severe ROP (international classification of ROP moderate or severe stage 3) occurs, synthesis and secretion of angiogenic factors stop, gap junctions between adjacent spindle cells disappear uniformly throughout the apron, the extensive volume of rough endoplasmic reticulum decreases, and all spindle cells stack within the inner retina The stimulus for the spindle cell stacking is unknown; this subclinical event indicates, however, that peripheral spindle cells are no longer the stimulus for neovascularisation and that severe ROP will either regress or progress for unknown reasons. When regression of severe ROP occurs, inner retinal vasoformation may occur between the stacked spindle cells, but this vasoformation is not by canalisation and does not reach the ora serrata. In some cases of regression of severe ROP, greyish remnants of the contractile myofibroblast sheets that are at the site of the former shunt are left behind along the retina vitreous surface as the only sequelae of the active ROP tabulated by international classification of ROP as mild peripheral, and posterior retinal and vascular changes.[10] In other cases these greyish remnants exist in sufficient numbers to cause dragging of the larger retinal vessels and of the macula. This is usually seen clinically as temporal dragging of the vessels and macula, tabulated by international classification of ROP as moderate peripheral, and posterior retinal and vascular changes.[10]

PROGRESSION

When progression of severe ROP occurs, synthesis and secretion of angiogenic factors stop, and all spindle cells stack. Clinically the posterior retinal vessels become dilated and tortuous (which is termed 'plus disease' according to international classification of ROP[9]), the shunt becomes engorged, and the myofibroblast sheets become vascularised and eventually haemorrhage into the vitreous (fig 6 top, fig 7 top, fig 8 top) Histologically a surge of myofibroblast sheets differentiate from the shunt and invade the vitreous (fig 9).

THE CONCEPT OF CRYOTHERAPY

Cryotherapy for ROP entails the application of a destructive cold probe to the scleral surface. The cold application must destroy both the spindle cells in the inner retinal layer and the myofibroblasts on the retina/vitreous surface. Cryotherapy destroys all living ocular tissue between the sclera and the retina/vitreous surface round the complete circumference of the eye. Fibroblasts from adjacent living sclera invade the dense scleral connective tissue residue, and allow anterior enlargement of the globe after cryotherapy

CRYOTHERAPY TO THE AVASCULAR RETINA FOR STAGE 2 OR MILD STAGE 3 ROP

Cryotherapy to the avascular retina when only neovascularisation is present, (that is when spindle cells are still secreting angiogenic factors and myofibroblasts have not separated from the shunt) has been suggested. Theoretically, obliteration of the peripheral inducers would stop the progression of the disease completely. Such early cryotherapy, however, may cause problems in the smallest infants. Many sessions of cryotherapy would be needed to obliterate spindle cells that were intermingled with the formed vessels at the time of the initial cryotherapy but which continue to migrate into the treated areas later, and there would be destruction of an appreciable amount of the peripheral visual field and possibly macular dragging in an eye that might have undergone spontaneous regression. Thus early cryotherapy (at ROP stage 2 or mild stage 3) is not recommended.

CRYOTHERAPY TO THE AVASCULAR RETINA FOR MODERATE OR SEVERE STAGE 3 ROP

The National Eye Institute of the National Institutes of Health in the United States of America sponsored a clinical trial to evaluate the effect of cryotherapy to the avascular retina for ROP in eyes randomised

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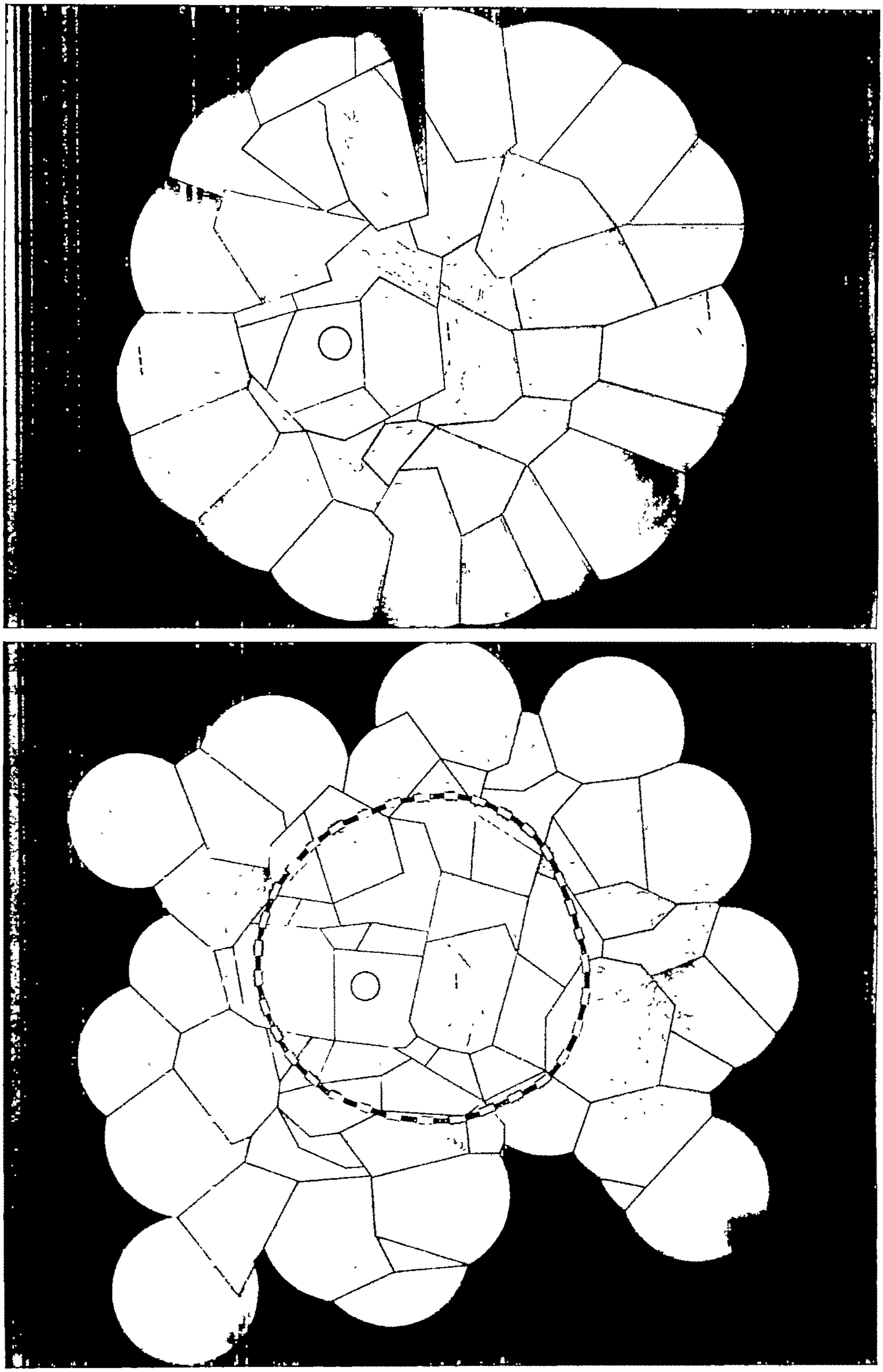
Fig 7 *Top: preoperative appearance at the age of 10 weeks of the right retina of an infant weighing 880 g at birth, with zone II stage 3+ ROP Note the extent of vascularised retina (distance between the pair of three vertical dashes equals 2·4 cm of retina); and immature macula (circle), and the distance between the temporal rim of the optic disc (two vertical dashes) and the centre of the macula equals 0·5 cm of retina Severe plus disease and an area of haemorrhage adjacent to severe invasion of myofibroblasts are visible Bottom postoperative appearance of the same eye at the age of 20 months. Note temporally displaced, abnormally pigmented macula (circle), the distance between the temporal rim of the optic disc (two vertical dashes) and the centre of the macula equals 0·6 cm of retina, and the anterior extent of the therapeutic scleral buckle (wide solid circular line). Fixation is unsteady (nystagmus) in this myopic (−9·50) eye. Comparison of these two retinal montages shows that cryotherapy to the avascular retina and shunt alone did not prevent retinal detachment, and that a therapeutic scleral buckle does not permit a favourable outcome with respect to macular function.*



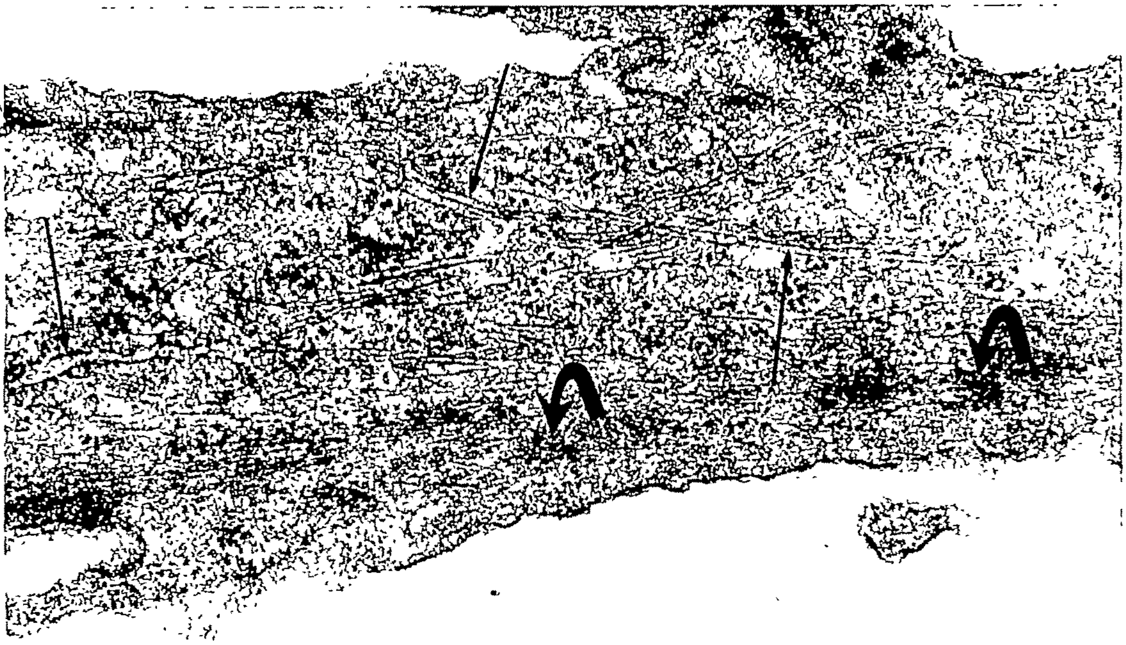


Fig 9 *Transmission electron micrograph of a myofibroblast with actin filaments (arrows) criss crossing the cytoplasm and ending in peripheral densities (curved arrows) that are analogous to Z lines of striated muscle (magnification of 48 000)*

in symmetrical disease or in randomised infants in asymmetrical disease. Threshold disease was the development of five or more contiguous or eight cumulative clock hours of stage 3 ROP in zone I or II in the presence of 'plus' disease. This clinical trial found that cryotherapy to the avascular retina (as determined by fundus photographs of outcome three months after treatment) reduced the number of posterior retinal detachments, retinal folds affecting the macula or retrolental tissue, by 50%.[23] Of 156 treated eyes, 22% had an unfavourable outcome (78% had a favourable outcome), and of 149 untreated eyes, 43% had an unfavourable outcome (57% had a favourable outcome). Thus neither vitamin E nor cryotherapy is a panacea.

Though this collaborative trial evaluated the effect of cryotherapy for ROP, many questions still remain unanswered. The mean birth weight for the study was 801 g and only 12 eyes (8%) had zone I ROP. It is unfortunate that the study will generate long term data only for comparatively large infants (92% had zone II ROP). According to the spindle cell/myofibroblast pathogenesis of ROP, if vitamin E supplementation for prevention of severe ROP had been given, many of the larger preterm infants might not have required cryotherapy, and the ratio of zone I : zone II disease would have been more equal. With increasing survival of the smallest preterm infants, however, the dilemmas of zone I disease cannot be addressed by the data base of this trial. Unfortunately the outcomes of zone I, which are more difficult to treat, were grouped with those

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Fig 8 *Top: preoperative appearance at the age of 10 weeks of the right retina of an infant weighing 760 g at birth with zone II stage 3+ ROP. Note the extent of vascularised retina (distance between the pair of three vertical dashes equals 2·4 cm of retina); and immature macula (circle), and the distance between the temporal rim of the optic disc (two vertical dashes) and the centre of the macula equals 0·5 cm of retina. Severe plus disease and an area of haemorrhage adjacent to severe invasion of myofibroblasts are visible. Bottom: postoperative appearance of the same eye at the age of 17 months. Note undisplaced, normally pigmented macula (circle), the distance between the temporal rim of the optic disc (two vertical dashes) and the centre of the macula equals 0·5 cm of retina, and the anterior extent of the prophylactic scleral buckle (wide dashed circular line). Fixation is steady (no nystagmus) in this myopic (−6·25) eye at the age of 18 months. Comparison of these two retinal montages shows that cryotherapy to the avascular retina and shunt combined with a prophylactic scleral buckle does permit a favourable outcome with respect to macular function.*

of zone II. The study reported treatment that ranged from 6·7 to 23·9 weeks. The timing of cryotherapy was at a mean of 11·4 weeks, however, which coincides with the window of treatment (generally 8 to 10 weeks, but occasionally 6 to 15 weeks) predicted by the spindle cell/myofibroblast pathogenesis of ROP. At the later time points (15 weeks or more), it is not stated how many eyes were treated or what the percentage of favourable outcomes was. Unfortunately the study grouped the percentage of favourable outcomes without regard to the timing of cryotherapy. Thus it is unknown how many eyes were treated primarily to prevent traction associated with myofibroblasts Despite a protocol designed to avoid the shunt, appreciable haemorrhages occurred in 30 eyes (19%). This high incidence was most likely caused by accidental cryotherapy to the shunt while it was still engorged with blood. Though it was important to expedite publication of the effectiveness of cryotherapy, only 45 infants had been followed for one year. Because of the developmental process of ocular growth (fig 4), the spindle cell/myofibroblast pathogenesis of ROP would predict that many of the reported successes will become failures with long term follow up. Tasman's editorial about the study has already alluded to this problem by describing rhegmatogenous retinal detachment in the better eye of two patients (at 1 and 4 years of age).[24] He attributes these retinal detachments to the intolerable stress associated with ocular growth that occurs after cryotherapy caused by a firm peripheral chorioretinal adhesion in small eyes. Our centre had a similar retinal detachment in the better eye of a patient (at 5 years of age).[25]

We realise that when the remnant myofibroblast sheets produce minimal traction, the single procedure as recommended by the collaborative group may be sufficient; the larger retinal vessels and macula can, however, be appreciably dragged by ocular growth, and visual acuity may be as low as 20/200. Frequently, when myofibroblast sheets produce appreciable traction, this single procedure is not sufficient to counterbalance the forces generated by an active contraction of myofibroblast sheets, by a fixed remnant myofibroblast ridge, or by ocular growth, and retinal detachment can occur. To obtain retinal reattachment, a therapeutic scleral buckle is required (often with drainage of subretinal fluid). Scleral buckling entails placing a thin (0·75 mm) but broad (3·5 mm) silicone band round the equator of the eye under the four rectus muscles. Even when the retina is successfully reattached anatomically, the macular region has a distorted clinical appearance, and the best visual acuity that can be anticipated is 20/400.

OUR CURRENT SURGICAL PROTOCOL

With our long experience of cryotherapy to the avascular retina (since 1974) and with the unfavourable visual outcome of most of the patients caused by macular dragging or retinal detachment, we have advocated since 1987 the following surgical operations based on both the spindle cell/myofibroblast pathogenesis of ROP and the reality of ocular growth.

Destroy the spindle cell apron that is the source of angiogenic factors. This part of our current protocol is identical to that recommended by the collaborative study except that we treat both eyes when symmetrical disease is present. Clinically, within a day or two after cryotherapy to the avascular retina, the posterior retinal vessels become less dilated and tortuous, the shunt empties of blood, and the sheets of myofibroblasts atrophy.

Destroy the shunt and sheets of myofibroblasts that are the source of traction leading to macular dragging or retinal detachment. This second cryotherapy to the shunt and sheets of myofibroblasts (optimally some three to seven days after the initial cryotherapy to the avascular retina) will produce less haemorrhage than might be produced if the shunt and sheets of myofibroblasts are inadvertently treated during the initial cryotherapy. The two treatments may be sufficient to prevent retinal detachment in some cases, but do not prevent dragging of the macula (fig 6 bottom). The two cryotherapies, however, may not in many cases be sufficient to prevent retinal detachment, and a therapeutic scleral buckle may be required to reattach the retina (fig 7 bottom).

Place a prophylactic scleral buckle at the site of the former shunt at the time of the second cryotherapy. With continued growth of the anterior portion of the eye, this band changes the general shape of the eye from a sphere to an ellipse so that the posterior portion of the eye in which the macula resides is not dragged. Additionally, this band counterbalances tractional forces from the active contraction of sheets of myofibroblasts or from a fixed inactive remnant myofibroblast ridge that can lead to retinal detachment even when the shunt has been obliterated.

This staged procedure seems to allow the macula to develop maximally without distortion from dragging or detachment, and visual acuity is usually better than 20/40 (fig 8 bottom). When myofibroblasts have completely disappeared from the vitreous, complete quiescence of ROP has been obtained. When ocular growth is complete (at about 18 months), it is usually safe to remove the scleral buckle and permit the eye to return to its normal spherical shape.

As successful as these drastic operations may be, this also is not a panacea, and is not the ultimate solution to the continuing saga of ROP. Thus the challenge remains to stabilise spindle cells before the initiation of the cascade of events recounted here—the spindle cell/myofibroblast pathogenesis of ROP as modified by ocular growth.

For the last 10 years this research has been supported by grants from the Retina Research Foundation, National Institutes of Health (EY-02607), Hoffmann-LaRoche Inc, Research to Prevent Blindness, The March of Dimes Birth Defects Foundation, The Retinitis Pigmentosa Foundation Fighting Blindness, The Farish Foundation, The Cullen Foundation, and The Lion's Eyes of Texas Eye Bank The light and transmission electron micrographs were taken by Rekha Mehta and Evelyn Brown We acknowledge the photographic expertise of Alex Kogan and Gilma Miranda

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Accepted 29 June 1988

Archives of Disease in Childhood, 1988, **63,** 1168–1174

Short reports

Antenatally diagnosed subdural haemorrhage in congenital factor X deficiency

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SUMMARY The presence of a subdural haemorrhage was observed in a fetus during antenatal ultrasound examination The infant was found to be a homozygote for factor X deficiency. Prompt recognition permitted replacement treatment from an early stage. Inherited coagulation disorders should be suspected when intracranial haemorrhage is detected antenatally.

Congenital factor X deficiency is a rare coagulation disorder with considerable heterogeneity in its clinical manifestations. Intracranial haemorrhage in early infancy has been observed in a small number of these patients, and this is often associated with a poor outcome.[1] Although antenatal intracranial haemorrhage (including subdural haemorrhage) occurs as an unusual complication of other coagulation defects,[2] it has never been found in association with this disorder. We report a girl with a subdural haemorrhage, diagnosed on ultrasound scans before birth, who was subsequently shown to have factor X deficiency.

Case report

The girl was born by caesarean section at 37 weeks' gestation. Her parents were first cousins and belonged to a family in which there had been a number of intermarriages. A male sibling had died at another hospital five years previously at 2 days of age from a hypoplastic left heart and had been noted to have an unidentified coagulopathy The mother, who had a history of easy bruising, was investigated at that time and found to have a prolonged prothrombin time (British comparative ratio 1·5) and concentrations of factor V of 86%, factor VII of 60%, and factor X of 41%. There was no other family history of a bleeding disorder.

In this pregnancy the mother had booked at 22 weeks' gestation. Details of her previous confinement and investigations were not known. An ultrasound scan had shown an appropriately grown fetus with no detectable abnormalities. The pregnancy proceeded uneventfully except for a minor fall down some stairs at 33 weeks. At 35 weeks, however, an ultrasound scan had shown a fluid collection with a straight medial border underlying the left parietal bone and a shift of the midline to the right. This appearance, which was thought to be due to a subdural haemorrhage, was seen on further ultrasound scans up to 37 weeks (fig 1). It did not appear to be enlarging. A caesarean section was performed in order to minimise trauma to the fetal head.

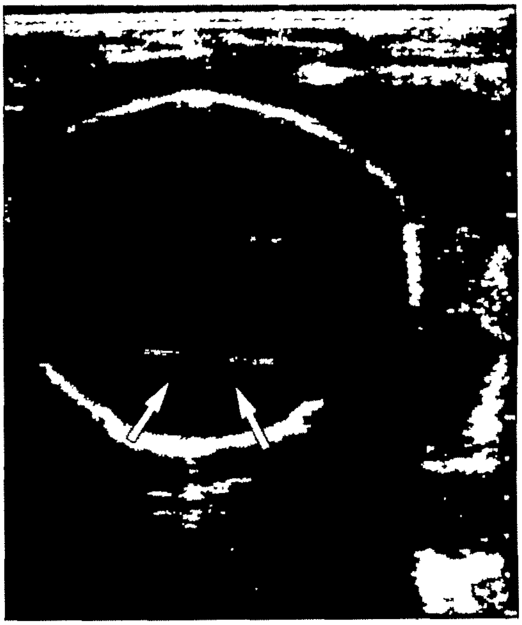

Fig 1 *Obstetric ultrasound scan at 37 weeks' gestation Fetal subdural haemorrhage is shown by the arrows.*

At birth the child weighed 2310 g and was clinically well with no evidence of a bleeding disorder. Head circumference was 33 cm, which is on the 50th centile. Cranial ultrasound and computed tomograms of the brain showed a large left subdural haemorrhage with compression of the left lateral ventricle (fig 2). Her packed cell volume and platelet count were normal. Coagulation studies were abnormal: prothrombin time >180 seconds (normal range 13·5–17), partial thromboplastin time 166 seconds (normal range 45–70), and reptilase time 27 seconds (normal <16) Factor X concentrations, measured by the one stage method for activated partial thromboplastin time (APTT), showed less than 1% activity, and <5% factor X antigen by Laurell immunoassay. Factor X concentrations in the normal newborn are generally lower than in older children and adults, usually around 50%. The mother's factor X concentration was 56% and her father's 63% when measured by the one stage APTT method, and 61% and 64% by Laurell immunoassay. These were characteristic of factor X deficiency in the patient and compatible with a heterozygote state in her parents. Specific assays for other clotting factors were normal.

She was treated with infusions of fresh frozen plasma and later with factor IX concentrate. Forty ml of bloodstained fluid were removed in total during three subdural taps. A further cranial computed tomogram at 2 weeks showed no evidence of reaccumulation of the subdural haemorrhage but a later scan at 4½ months of age showed left hemispheric atrophy and a persistent supratentorial midline cyst. Neurological examination at this and later stages was normal with no evidence of any focal deficit. In the succeeding weeks she had a number of episodes of gastrointestinal bleeding and epistaxis that required treatment with factor IX concentrate and blood transfusion. At 2 months of age she was started on a regime of weekly infusions of factor IX concentrate. Although this was not sufficient to maintain her factor X concentration at more than a few per cent for much of the time, she had no further episodes of haemorrhage. She was growing and developing normally with a normal head circumference. At 7 months of age, however, she sustained a new and extensive intracerebral haemorrhage affecting the frontal and parietal regions and died.

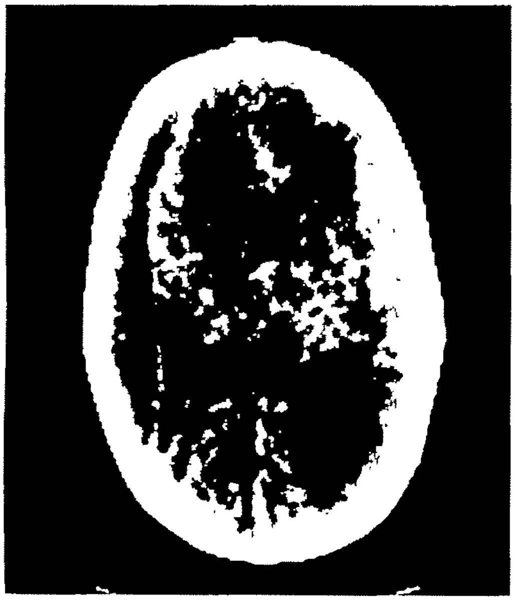

Fig 2 *Computed tomogram at 2 days of age There is a large left subdural haemorrhage with compression of the left lateral ventricle.*

Discussion

Factor X is involved in the formation of prothrombin and is activated by both the extrinsic and intrinsic coagulation pathways. Congenital factor X deficiency is inherited as an autosomal incompletely recessive condition. Immunological and other coagulation methods have shown a number of different forms of factor X defect. Most homozygotes will suffer from minor complications such as easy bruising, haematoma formation, and epistaxes but more serious manifestations including haemarthroses, gastrointestinal bleeding, and cerebral haemorrhage are seen in a small proportion.[3] There are reports of intracranial haemorrhage occurring in infants with factor X deficiency,[1] and in one case haemorrhage occurred in the neonatal period.[4] Our case is the first in which antenatal haemorrhage has been identified.

Treatment by infusions of fresh frozen plasma or factor IX concentrate, which contains appreciable amounts of factor X (around 30 units per ml), is successful in raising the concentrations of factor X and in preventing excessive bleeding in adult patients[5] Despite regular prophylactic treatment, infants with the disorder often suffer from major and potentially fatal episodes of haemorrhage including intracranial haemorrhage.[1 4] It is possible that these patients, who present earliest in life, have a more severe variant of the disorder.

Antenatal intracranial haemorrhage is a rare complication of coagulation disorders. It has been found in fetal thrombocytopenia, in the infant of a mother who received warfarin throughout pregnancy, and in congenital factor V deficiency[2] Fetal subdural haemorrhage due to any cause is extremely rare. It may occur after maternal trauma, although it is rare in the absence of skull fractures or other severe fetal or maternal injuries [6]

This patient's clotting disorder rendered her more liable to haemorrhage after minor trauma Her mother's fall down stairs at 33 weeks' gestation was a likely cause of her subdural haemorrhage. Because the haemorrhage had been detected antenatally it was possible to deliver the infant by caesarean section, thus minimising the risk of further trauma. This also permitted a diagnosis to be arrived at and treatment to be instituted within hours of birth. This case emphasises the importance of recognising intracranial haemorrhage on obstetric ultrasound, and the need to identify potentially treatable coagulation disorders in such patients. In some disorders, such as this one, it should be possible to arrive at a diagnosis even before delivery, thus optimising management in the postnatal period

We thank Professor MG Elder and Dr M Silverman for permission to report these patients who were under their care

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Accepted 13 April 1988

Weight, length, and head circumference curves for boys and girls of between 20 and 42 weeks' gestation

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SUMMARY The value of available growth curves for preterm infants is limited because they exclude infants of less than 28 weeks' gestation. We describe growth curves for weight length, and head circumference for boys and girls of between 20 and 42 weeks' gestation.

We have previously reported an analysis of fetal and infant birth weights derived from data from Sheffield from 1976 to 1984, and compiled a weight chart for those between 20 and 42 weeks' gestation [1] At certain gestational ages there were significant differences between our data and the weight curves in current use, and subsequently the Gairdner-Pearson chart was revised using this and other data.[2]

Despite the considerable developments in neonatology resulting in the treatment of increasing numbers of infants born at less than 28 weeks' gestation, the practical value of most of the available growth charts is limited by the exclusion of this group of infants. We have therefore expanded our data to include length and head circumference and produced a comprehensive chart suitable for use in neonatal units.

Sample and methods

The sample was derived from three subgroups from the Sheffield area· live born infants, fetuses from therapeutic abortions, and fetuses from spontaneous abortions; only morphologically normal singletons were included. The following were excluded: hydropic infants, infants of diabetic mothers, and macerated fetuses. The previously published data were expanded to include fetuses and infants born in 1984 and 1985 at between 20 and 28 weeks' gestation in four local maternity units. This increased the total number of fetuses and infants below 28 weeks' gestation from 192 to 281 and enabled us to provide separate curves for boys and girls.

The data were taken retrospectively from the babies' records. All babies were weighed and measured while still on the labour ward or directly after admission to the special care baby unit. Dead fetuses were measured at necropsy, which usually took place within 48 hours of delivery. The curves for dead fetuses did not deviate from those of live born infants, so the figures for the two groups were amalgamated for analysis. Gestational age was calculated by comparing estimations of time from last menstrual period, by study of early antenatal ultrasound scans, and by the Dubowitz score, or pathological examination. Where there was any ambiguity, the anthropometric data were excluded.

Means and standard deviations were calculated for weight, length, and head circumference at each completed week of gestation. Calculations were made for the whole group, and for boys and girls separately.

Results

The means for the whole group are in close accord with those reported by Kitchen *et al* for between 24 and 42 weeks' gestation [3] Although size differences between boys and girls were apparent by the third trimester they could not be distinguished graphically until about 32 weeks' gestation.

The raw data are shown in the table and the smoothed curves constructed from those data in figs 1 and 2.

Discussion

We recognise that the use of cross sectional data in the derivation of postnatal growth norms for preterm infants has inherent weaknesses. This is particularly apparent for head circumference, and caution should be exercised when any such chart is used to assess growth longitudinally.[4] Almost all the data from which published charts are compiled have excluded some infants. We excluded hydropic infants, infants of diabetic mothers, and macerated fetuses. We thought it appropriate, however, to include morphologically normal babies who were thought to have retardation of growth before delivery; their exclusion would have biased the results. Previous studies, for example Gruenwald,[5] have excluded babies whose measurements were at the extremes of the range, usually because of the lack of certainty about gestational age. We were more certain of the gestational ages of the babies in our studies and so have not excluded extreme measurements; nor have we excluded babies from ethnic minorities. These made up less than 5% of the total sample and so their data are unlikely to cause bias. We believe that these charts may be of practical use in neonatal units, especially those dealing with extremely premature infants.

Table *Means (SD) weight, length, and head circumference by week of gestation*

Gestation (weeks)	*No*	*Weight (g)*		*Length (cm)*		*Head circumference (cm)*	
20	49	340(54)		26·4(2·2)		18·6(0·5)	
21	28	455(90)		27·0(0·8)		21·0(0·8)	
22	20	508(97)		29·6(0·6)		27·0(1·1)	
23	21	575(63)		31·3(2·4)		21·3(1·3)	
24	24	676(115)		31·3(2·1)		22·0(1·5)	
25	37	752(117)		33·3(2·1)		23·4(1·1)	
26	51	909(155)		33·8(2·7)		24·2(1·4)	
27	51	1083(130)		37·6(2·3)		25·8(1·1)	
28	85	1126(227)		37·2(3·2)		26·3(1·4)	
29	52	1285(203)		38·4(2·6)		26·7(1·2)	
30	89	1433(404)		41·4(3·3)		28·4(3·1)	
31	60	1547(241)		40·2(4·4)		28·8(1·0)	
		*Boys	Girls	Boys	Girls	Boys	Girls
32	101	1894(423)	1523(320)	44·6(4·5)	41·3(4·3)	30·5(2·3)	29·6(4·3)
33	114	2020(376)	1696(365)	44·7(3·0)	42·4(4·0)	30·7(1·3)	29·6(2·4)
34	156	2177(431)	1960(329)	46·8(4·3)	45·8(2·9)	32·1(1·8)	31·1(1·2)
35	60	2588(347)	2592(452)	47·1(4·4)	49·3(1·6)	33·4(1·2)	32·8(1·3)
36	60	2640(298)	2693(467)	48·2(2·2)	47·5(3·8)	33·2(1·2)	33·1(1·4)
37	60	3047(431)	2945(365)	50·4(2·4)	50·2(3·0)	34·3(0·9)	33·9(1·2)
38	120	3350(422)	3130(394)	52·2(2·3)	51·1(3·1)	35·0(1·2)	34·0(1·5)
39	120	3527(502)	3379(497)	51·9(3·2)	51·8(2·9)	35·2(1·4)	34·4(1·2)
40	120	3726(341)	3438(334)	53·7(2·3)	52·7(1·8)	35·6(0·9)	34·7(1·2)
41	60	3584(409)	3467(537)	53·2(2·8)	53·0(2·7)	35·9(1·2)	34·8(1·4)
42	60	3788(429)	3599(483)	54·5(3·6)	53·2(2·5)	35·5(1·2)	35·2(1·2)

*We could not distinguish accurately between boys and girls until 32 weeks' gestation

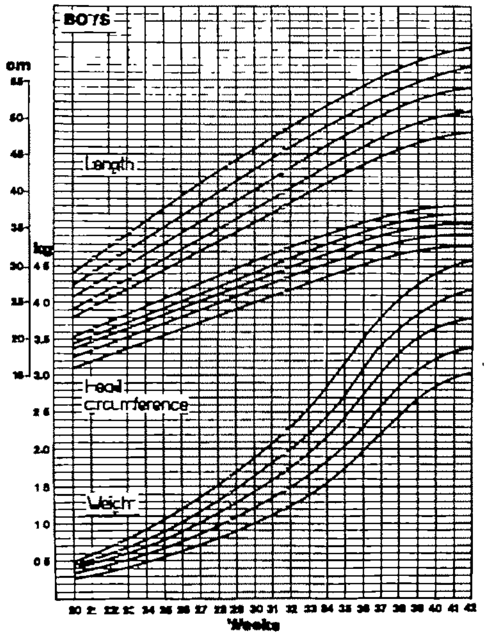

Fig 1 *Growth parameters boys (means±1 and 2 SDs)*

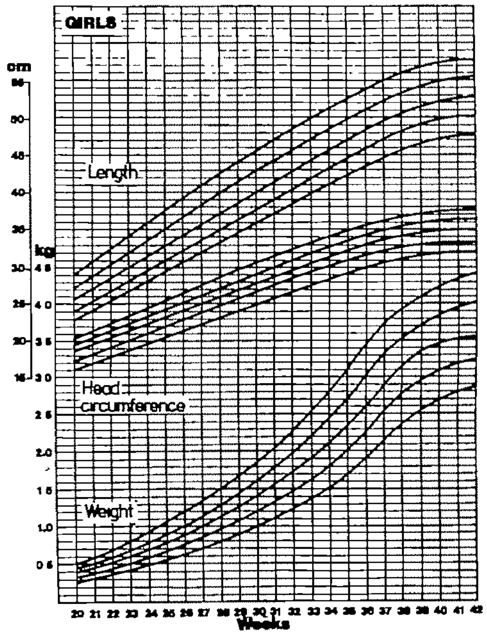

Fig 2 *Growth parameters: girls (means±1 and 2 SDs).*

We thank Mrs P Kenyon for her assistance in collecting the data, and Dr RP Beechey for computer processing

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Accepted 3 February 1988

Pansystolic murmur in the newborn: tricuspid regurgitation versus ventricular septal defect

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SUMMARY Neonates with a pansystolic murmur who had Doppler echocardiography were reviewed. Ten infants had tricuspid regurgitation (detected at a mean age of 25 hours), 12 had a ventricular septal defect (detected at 65 hours), and seven had both. Tricuspid regurgitation is the more likely cause of a pansystolic murmur at the lower left sternal border in the first day of life.

When we began peforming Doppler echocardiography in neonates with murmurs that suggested a ventricular septal defect, we found that many of them had neither an image of a ventricular septal defect nor flow disturbance; instead, we found turbulent systolic flow of tricuspid regurgitation. Further, we had the impression that the infants with tricuspid regurgitation had the onset of murmurs during the first day of life. We decided to investigate this in all newborn infants in our hospital who were shown to have a ventricular septal defect or transient tricuspid regurgitation.

Subjects and methods

All infants born at the University of Washington Hospital over the past four years who had a pansystolic murmur were subjected to the same protocol This comprised an immediate examination by the admitting nurse, including cardiac auscultation, and by a paediatric resident at once if there was any evidence of distress, but in any case by 12 hours of age. Nursing staff auscultated for heart rate at four hour intervals until the infant was stable, and at eight hour intervals thereafter. Doppler echocardiograms were performed with an Advanced Technology Laboratories Mark 600 echocardiograph. Standard methods were used for detection of the ventricular septal defect[1] and tricuspid regurgitation.[2] We did not include in the group with tricuspid regurgitation those infants who had minimal tricuspid regurgitation with a jet found only close to the tricuspid valve and extending less than 1 or 2 mm into the right atrium, as this degree of tricuspid regurgitation is present in many normal infants and is not audible at the chest wall. The age of each infant in hours at the time of discovery of the murmur was recorded. For infants whose murmur was discovered after 5 days of age, we assigned a maximal figure of 120 hours for purposes of comparison, to avoid excessive weighting by outliers. *t* Scores were calculated for the means and the confidence level determined using a two tailed table.

Results

Ten infants had tricuspid regurgitation only; their mean (SD) age at the time of detection of their murmur was 25·2 (41·0) hours. Twelve infants had a ventricular septal defect only; the mean (SD) age of detection was 65·17 (31·3) hours. Seven infants had both a ventricular septal defect and tricuspid regurgitation; the mean (SD) age of detection was 35·93 (34·8) hours.

The difference between the mean time of detection for the infants with transient tricuspid regurgitation and those with ventricular septal defect was 40 hours ($p<0.02$). There was a mean 10·7 hour delay for the discovery of the ventricular septal defect+tricuspid regurgitation group after the detection of the tricuspid regurgitation group. The difference in means between the ventricular septal defect+tricuspid regurgitation group and the ventricular septal defect group, 29·2 hours, almost achieved significance ($p>0.05$ but <0.1).

Discussion

Tricuspid regurgitation in the adult or child without pulmonary hypertension produces a murmur that is not high pitched,[3] and unless there is substantial regurgitation, the murmur will be soft and frequently inaudible, reflecting the normally low pressure gradient between the right ventricle and right atrium. In the presence of pulmonary hypertension the pressure gradient in tricuspid regurgitation may approach or exceed the gradient involved in a ventricular septal defect, resulting in a murmur that is indistinguishable from that of a small ventricular septal defect.

In the newborn, the pulmonary artery pressure is high immediately after birth, falls quickly in the first

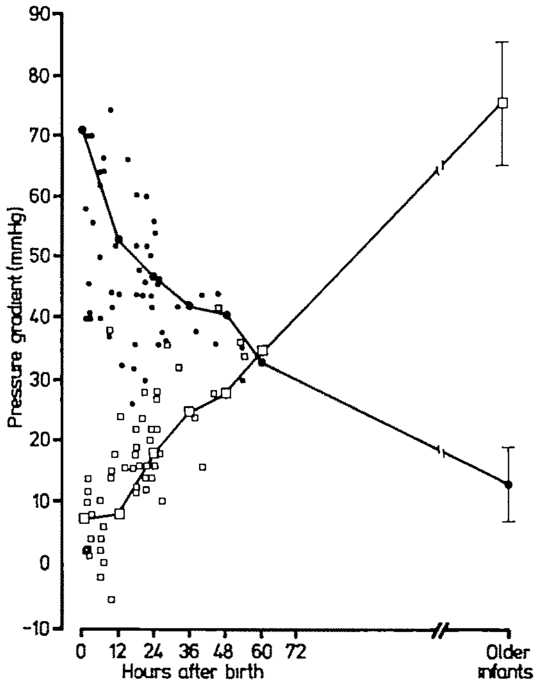

Figure *Pressure gradients in normal newborns calculated from data of Emmanouilides et al.*[4] *The solid circles represent the systolic gradient between the right ventricle and right atrium in 51 infants studied at the specified age The open squares represent individual values for the systolic pressure gradient between the left ventricle and right ventricle in the same subjects. The descending line represents the average force that could drive tricuspid regurgitation, and the ascending line the average force that could cause left-to-right flow through a small ventricular septal defect The large circles and squares on the two lines are the mean values for all points in the preceding 12 hour interval The last data points, with vertical bars, represent the mean and range of normal for 'newborn' published by Rudolph.*[5]

3 days,[4] and continues to fall for several weeks.[5] The initially high pulmonary artery pressure will increase the pressure gradient between the right ventricle and right atrium. The figure shows a plot of the pressure gradients calculated by us for tricuspid regurgitation in 51 normal infants catheterised during the first 3 days of life. The calculations are based on the 1964 data of Emmanouilides *et al*[4] and Rudolph.[5] During the first 24 hours the mean (SD) normal systolic pressure gradient between the right ventricle and atrium is 53 (12) mm Hg, and by 60 hours has dropped to 33 (14).

Similarly, plots of pressure gradients between the left ventricle and right ventricle in normal newborn infants calculated by us from the same data[4] show a very low gradient at birth (figure). During the first 24 hours, the mean (SD) systolic gradient is 8 (9) mm Hg, and by 60 hours has risen to 35 mm Hg. These data provide the physical basis for the delay in detection of the murmur of a ventricular septal defect in the neonate, namely the absence of a significant pressure gradient. even with very small ventricular septal defects

None of our patients with tricuspid regurgitation had any structural deformity of the tricuspid valve, and none of the murmurs persisted after the neonatal period. Dilatation of the right ventricle and the tricuspid annulus is the most frequent mechanism for tricuspid regurgitation in adults without structural heart disease.[6] Our undocumented impression was that some degree of stress was common in patients at the time of their transient tricuspid regurgitation.

We conclude that transient tricuspid regurgitation occurs frequently in a hospital with a high risk obstetrical programme, at least as often as ventricular septal defects. It is a more likely cause of a pansystolic murmur in the first day of life than a ventricular septal defect.

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Accepted 3 May 1988

Archives of Disease in Childhood, 1988, **63,** 1175–1178

Current topic

Prenatal diagnosis of skin diseases

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The possibility of prenatal diagnosis and abortion of abnormal fetuses reassures many couples considering a pregnancy. Some children are conceived only because the pregnancy can be terminated if a serious uncorrectable abnormality carried in the family is passed on. This paper reviews how skin diseases can be diagnosed prenatally. Space does not permit reference to most of the original papers but there are full recent reviews on this subject.[1-3]

Techniques of prenatal diagnosis

(1) STUDIES OF MATERNAL BLOOD

Maternal serum α fetoprotein concentration is used to screen for fetal defects which involve a break in fetal surface, such as spina bifida or exomphalos. It was hoped that this test would detect fetuses with blistering skin conditions such as epidermolysis bullosa. This technique has not proved useful for these conditions, however, and couples at risk of a severe skin disorder should not be over-reassured by a normal α fetoprotein concentration.

A possibility for the future is to use cell separating techniques to isolate the small number of fetal cells found in maternal blood. This would allow prenatal diagnosis by the techniques described in section 3 without instrumenting the uterus.

(2) ULTRASOUND IMAGING

The skin itself is not an organ easily examined by ultrasound scanning. Syndromes that include skeletal or other structural defects, however, can be diagnosed by ultrasound scanning alone For example, severely affected fetuses with Goltz's syndrome (focal dermal hypoplasia), X linked chondrodysplasia punctata, and Ellis-van Creveld syndrome (chondroectodermal dysplasia) will manifest limb abnormalities, which can be diagnosed by ultrasound examination at about 18 weeks' gestation. Fetal sexing is often possible by ultrasound and if this shows a fetus is female, invasive diagnostic tests for X linked conditions may be unnecessary.

Ultrasound scanning plays an important part in all invasive prenatal diagnostic procedures. Although successful fetal sampling has been described using endoscopic or 'blind' techniques, transabdominal ultrasound guided needling has replaced these methods.[4-6] By holding the ultrasound transducer parallel to the proposed path of the needle, it is possible to identify the target, observe the needle enter the skin, and then guide the needle to the target through a safe route [6] This technique is used to obtain amniotic fluid (amniocentesis), chorionic villi (placental biopsy), fetal blood (cordocentesis), and biopsies of fetal tissues. For fetal skin biopsy, cupped biopsy forceps (figure) are passed down the needle, opened, pressed on to the fetal skin, closed, and the forceps are then withdrawn through the needle All of these tests are done as outpatient procedures in an ultrasound clinic under local anaesthetic and without maternal sedation

As these tests are all done in the same way, they are thought to have a similar procedure related risk of causing fetal death, which in experienced hands is about 1%.[5 7 8] The risk of a pregnancy miscarrying after an invasive test, however, is also determined by the spontaneous abortion rate, which depends on the gestational age, obstetric history, indication for prenatal diagnosis, and many other factors but can be much greater than 1%. In those fetuses surviving to delivery at term a fetal skin biopsy site is either not detectable at birth or perhaps a very small scar is occasionally produced.

Ultrasound guided needling of the pregnant uterus is associated with almost no serious maternal complications Fetomaternal haemorrhage does sometimes occur and so rhesus negative mothers are given an injection of human anti-D immunoglobulin. Despite this precaution maternal red cell isoimmunisation to D or other red cell antigens will occasionally be produced.

(3) STUDIES OF FETAL CELLS (AMNIOCYTES OR CHORIONIC VILLI)

Fetal cells are usually obtained for prenatal diagnosis by amniocentesis or placental biopsy (see above)

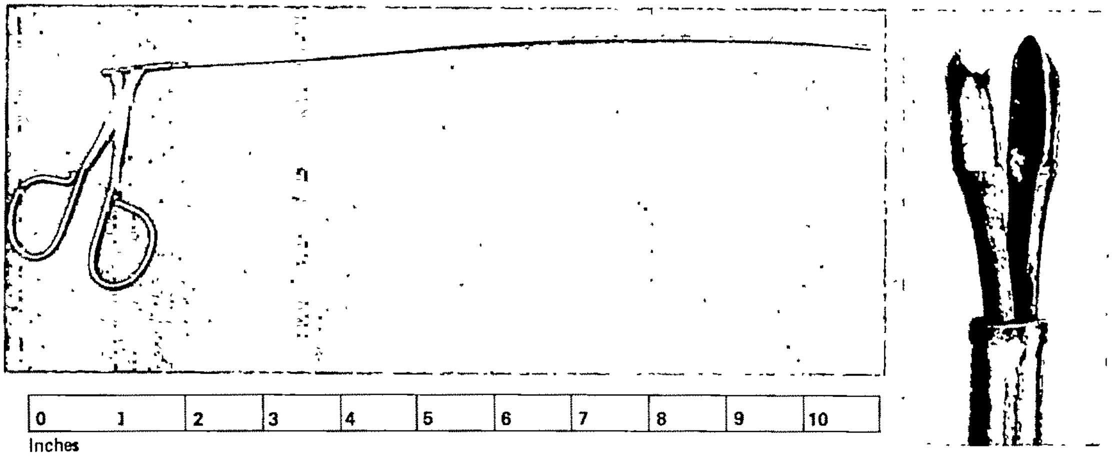

Figure *Fetal skin biopsy forceps. The cupped tip is drawn in or out of the sleeve by opening or closing the handles*

Initially amniocentesis was done after 14 weeks' gestation and placental biopsy before 12 weeks but both these gestational age limits have been challenged and these tissues can be used over a wide range of gestational ages.[5 6] The great advantage of fetal cell techniques in prenatal diagnosis, however, is that they can be used earlier in pregnancy than the other approaches currently available

(a) Cytogenetics

Structural abnormalities of chromosomes can be identified at the metaphase stage of cell division The number of cells in metaphase can be increased by cell culture and by incubation with colchicine. These steps are usually needed with amniocytes, but the number of fetal cells obtained and the incidence of cell division is higher with chorionic villi so that a 'direct' cytogenetic preparation can be made and gross abnormalities like Down's syndrome can be excluded within a day.

Fetal sexing and abortion of male fetuses can be used in the case of X linked diseases for which there is as yet no specific diagnostic test (for example, incontinentia pigmenti). Alternatively, if the fetus is shown to be female further investigation—such as skin biopsy to diagnose X linked hypohidrotic ectodermal dysplasia—is unnecessary More detailed cytogenetic analysis including chromosome banding, which usually requires a period of cell culture with both amniocytes and chorionic villi, can allow identification of structural abnormalities of the chromosomes associated with clinical syndromes. Ataxia telangiectasia can be diagnosed by increased spontaneous chromosomal breakage especially at a particular site on chromosome 14. Bloom's syndrome features an increased sister chromatid exchange rate, xeroderma pigmentosum has defective DNA repair after ultraviolet irradiation, and Cockayne's syndrome cells are extremely sensitive to the cytotoxic effect of ultraviolet irradiation but show normal DNA repair.

(b) DNA analysis

Every nucleated cell contains the entire genome Therefore, tests which involve study of the genome can be done using nucleated cells from any tissue. Some diseases are always produced by a known single base mutation so that fetal cells can be examined for this and no family studies are required Usually, however, only the region of a chromosome that contains the mutation can be detected This is done by studying each family requesting prenatal diagnosis to see whether inheritance of an identifiable region of DNA is associated with inheritance of the disease ('gene tracking'). When this is the case the family is described as informative and prenatal diagnosis is possible as soon as fetal cells are available (from eight to nine weeks' gestation onwards) Conditions with skin manifestations in which this can be done include Von Recklinghausen's neurofibromatosis, tuberous sclerosis, hypohidrotic ectodermal dysplasia, and dyskeratosis congenita.[10] X linked ichythyosis has been mapped and the mutation (a deletion) detected in many cases but it is unlikely that parents would want prenatal diagnosis for this condition.

Rapid extension of these techniques to the prenatal diagnosis of a wide range of severe skin disorders is expected. Gene mapping requires a large number of cases, however, especially to exclude heterogeneity in the mutation locus, and many of the skin disorders for which prenatal diagnosis could be requested are rare. International collaboration is required to facilitate these advances.[10]

(c) Biochemical studies

Unlike the genome, biochemical functions are not always present in every cell However, biochemical properties of fetal cells can sometimes be used for prenatal diagnosis When it has been shown that an enzyme is normally produced by amniocytes or chorionic villi at the appropriate gestational age and the absence or reduction of enzyme activity in these tissues is associated with the disease, prenatal diagnosis is possible Enzyme defects that can be diagnosed prenatally in this way include Ehlers-Danlos syndrome type VI (lysyl hydroxylase) and type VII (procollagen peptidase), X linked cutis laxa (lysyl oxidase), congenital erythropoietic porphyria (uroporphyrinogen III cosynthetase), Fabry's disease (α galactosidase), and α L fructose deficiency. Other metabolic disorders manifest in fetal cells that can be used for prenatal diagnosis include increased uptake of radiolabelled copper in Menkes' syndrome.

(d) Exfoliative cytology

As many amniotic fluid cells are desquamated skin cells, it was hoped that study of these would allow prenatal diagnosis of skin disorders. This may be possible in the diagnosis of bullous congenital ichthyosiform erythroderma but so far this technique has not been used because of problems with blood cell contamination, changes with gestational age and the large number of cell types found in amniotic fluid.[2]

(4) STUDIES OF FETAL BLOOD

Cordocentesis has a limited role for prenatal diagnosis of skin disorders. Syndromes which include skin manifestations that are diagnosable prenatally by studies of fetal blood include the Wiskott-Aldrich syndrome (abnormal platelets), the Chédiak-Higashi syndrome (ultrastructural abnormalities of neutrophils), and the Heamansky Pudlak syndrome (ultrastructural abnormalities of platelets and monocytes).

(5) FETAL SKIN STRUCTURE

Prenatal diagnosis of most skin disorders will eventually be done by the techniques described above rather than fetal skin biopsy. This is because fetal skin is not sufficiently mature for such diagnosis until an advanced gestational age for subsequent abortion should the fetus be found to be affected. Until earlier diagnosis is possible, however, these techniques will continue to prove extremely useful and acceptable to many families at risk of severe skin disease. It is essential that before undertaking prenatal diagnosis by fetal skin structure there should be good communication between the obstetrician and dermatologist and that during the biopsy procedure the skin samples should be confirmed as adequate by an experienced microscopist.

(a) Epidermal disorders

Keratinisation normally starts at 24–26 weeks. Fortunately, some keratinisation diseases can be recognised at 20–22 weeks' gestation because of characteristic skin structures (bullous ichthyosiform erythroderma) or because of an abnormally early onset of keratinisation (Harlequin ichthyosis, lamellar ichthyosis, and Sjogren-Larsson syndrome).

(b) Epidermolysis bullosa syndromes

The structural components of the dermoepidermal junction start to develop in the first trimester of pregnancy. Prenatal diagnosis is usually done from 18–22 weeks but diagnosis of some of these conditions as early as 15 weeks has been reported. Both junctional and dystrophic types of epidermolysis bullosa, and the Dowling variety of epidermolysis bullosa simplex can be diagnosed by their characteristic planes of separation with ultrastructural abnormalities and by the use of direct immunofluoresence using monoclonal antibodies specific for junctional antigens.

(c) Ectodermal dysplasias

X linked hypohidrotic ectodermal dysplasia can be detected by absence of pilosebaceous units in fetal skin at 20 weeks' gestation, but can now often be diagnosed by use of gene tracking.

(d) Albinism

Tyrosinase negative oculocutaneous albinism can be diagnosed by ultrastructural examination of hair bulb melanosomes in biopsy specimens of fetal scalp at 18–20 weeks' gestation.

Conclusion

The decisions as to whether the risk of having an affected child justifies prenatal diagnosis and whether the consequences of the disease indicate abortion of an affected fetus must be taken by the parents after obtaining as much information as possible about the disease and the procedures. Some of the conditions now diagnosed only in the second trimester will in the future be detectable in the first trimester, and the number of diseases for which prenatal diagnosis can be offered will increase. Doctors advising couples at risk of having a child with a severe inherited disease should consider referral for investigations such as family DNA studies, which might allow a diagnosis earlier in the pregnancy Information about these techniques might allow them to consider a pregnancy which they would otherwise not contemplate.

I am very grateful to Dr D Atherton for advice during the preparation of this manuscript

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ISSN 0003–9888 ASTM CODEN: ADCHAK 63(10), 1119–1178, (1988)

29.11.90

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BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

ISSN 0003-9888 ASTM CODEN ADCHAK 63(11), 1301–1422, (1988)

Archives of Disease in Childhood

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Elborn and M.M. Kerr. June 1982 Midwives Chronicle and Nursing Notes p. 210 – 211

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18 - 30 June 1989, London

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The topics covered in the course will include the following:

The pattern of normal development; the range and variations of normal development; the factors affecting development; the methods used to detect and quantify abnormal development; the theories of development; observation techniques; sensory examination and assessment; the development of children with abnormalities; the organization of child development services and what, when, how and by whom should development work be done.

The course will be directed by **Professor K S Holt**, Head of the Department of Developmental Paediatrics, Institute of Child Health, University of London, and Director of the Wolfson Centre.

The course is designed for paediatricians who are concerned with child development work either in practice or in planning services. Although attention will be given to children with developmental problems it will not be possible to cover all aspects of childhood rehabilitation in detail. Participants should have experience of working with children and should be able to discuss their work.

There are vacancies for 30 members.

Fee: £1,425 residential,
£995 non-residential.

Course sessions are expected to take place at the Institute of Child Health. Resident participants will be accommodated at a hotel within easy reach of the Institute.

The British Council

Further information and application forms are available from British Council Representatives overseas or from
Courses Department,
The British Council,
65 Davies Street,
London W1Y 2AA.

Abbreviated Prescribing Information
'HUMULIN' S ▼ 'HUMULIN' I ▼ 'HUMULIN' Lente ▼ 'HUMULIN' Zn ▼ 'HUMULIN' M1 ▼ 'HUMULIN' M2 ▼ 'HUMULIN' M3 ▼ 'HUMULIN' M4 ▼ Human insulin (prb). **Presentation: Humulin S:** A sterile, aqueous solution of human insulin (prb). **Humulin I:** A sterile suspension of isophane human insulin (prb). **Humulin Lente:** A sterile suspension of 30% amorphous and 70% crystalline human insulin (prb) zinc suspension. **Humulin Zn:** A sterile suspension of crystalline human insulin (prb) zinc suspension. **Humulin M1:** A sterile suspension of human insulin (prb) in the proportion of 10% soluble insulin and 90% isophane insulin. **Humulin M2:** A sterile suspension of human insulin (prb) in the proportion of 20% soluble insulin and 80% isophane insulin. **Humulin M3:** A sterile suspension of human insulin (prb) in the proportion of 30% soluble insulin and 70% isophane insulin. **Humulin M4:** A sterile suspension of human insulin (prb) in the proportion of 40% soluble insulin and 60% isophane insulin. Each presentation contains 100 IU/ml. **Uses:** For the treatment of insulin-dependent diabetes mellitus. **Dosage and Administration:** The dosage should be determined by the physician, according to the requirements of the patient. All Humulin preparations may be given by subcutaneous or intramuscular injection, but only Humulin S may be given intravenously. Humulin S may be administered in combination with Humulin I, Humulin Lente or Humulin Zn as required. **Humulin I, Lente, Zn, M1, M2, M3 and M4:** Rotate vial in palms of hands immediately before use to resuspend. Do not shake vigorously. **Mi**
of insulins: The shorter-acting insulin should
drawn into the syringe first, to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediate
after mixing. **Contra-indications, Warning**
etc. Contra-indications: Hypoglycaemia.
no circumstances should any Humulin preparation, except Humulin S, be given intravenously. **Precautions: Usage in pregnancy:** Insulin requirements usually fall
during the first trimester and increase during
second and third trimesters. **Transferring f**
other insulins: A small number of patients transferring from insulins of animal origin ma
require a reduced dosage and/or a change in ratio of soluble to intermediate preparations, especially if they are very tightly controlled an
bordering on hypoglycaemia. The risk of hypoglycaemia can be considered minimal if
daily dosage is less than 40 IU. Insulin-resista
patients receiving more than 100 IU daily sho
be referred to hospital for transfer. **Side-effe**
Lipodystrophy, insulin resistance and hypersensitivity have rarely been reported. **L**
Category: P. **Package Quantities:** 10ml g
vials in packs of 5. **Price:** All formulations £6
per 10ml vial. **Product Licence Numbers:**
Humulin S 100/IU/ml 0006/0216, Humulin I
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0006/0224, Humulin Zn 100/IU/ml 0006/0
Humulin M1 100/IU/ml 0006/0220, Humuli
100/IU/ml 0006/0222, Humulin M3 100/IU/
0006/0233, Humulin M4 100/IU/ml 0006/0
Date of Preparation: January 1987.

Full Prescribing Information Available From: Eli Lilly and Company Limited,
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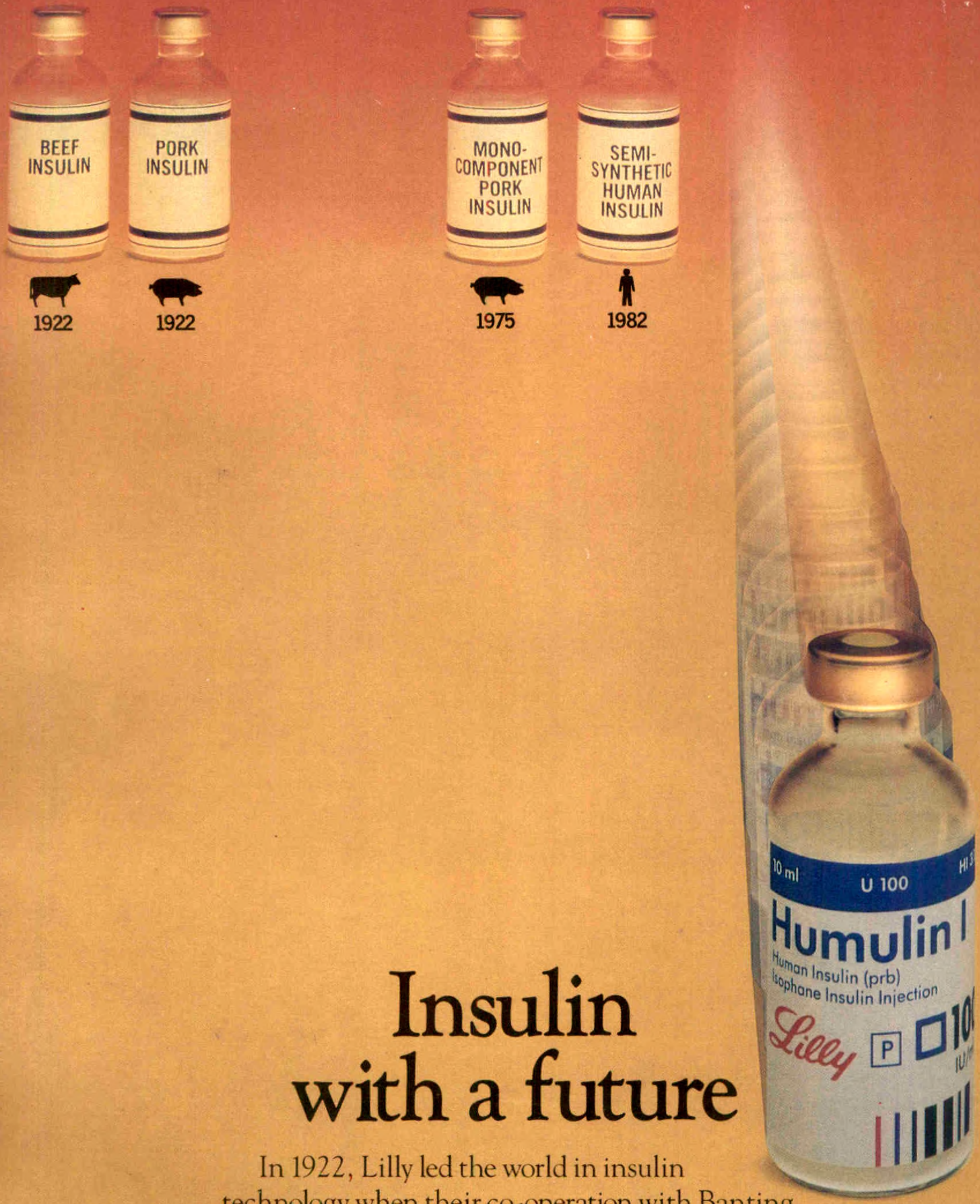

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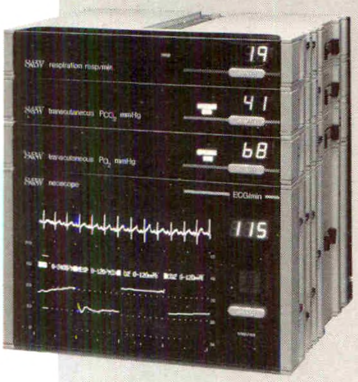
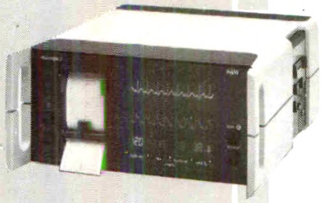
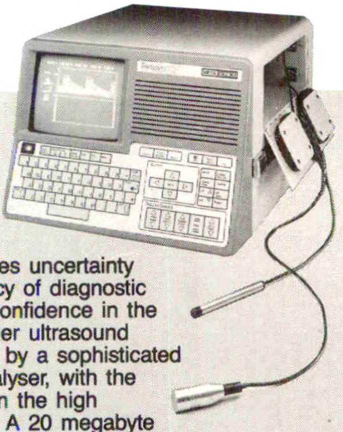

S&W respiration resp/min
19
S&W transcutaneous P_{CO_2} mmHg
41
S&W transcutaneous P_{O_2} mmHg
68
S&W neoscope
ECG/min
115

The Neoscope has been designed specifically for neonatal use, with capabilities of displaying 3 dynamic wave forms, or 3 separate cardiorespirogram options. The modular design concept of the Neoscope system offers full flexibility at an affordable price, with modules available for all standard neonatal parameters.



The Diascope 2 is ideal where less sophisticated monitoring is required. All units include E.C.G. and temperature as standard, with options available for invasive pressure or respiration. The Diascope 2 can also be specified with an integral recorder. Used with optional integral batteries, it is particularly suitable when transferring neonates either externally between hospitals, or internally between departments.



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Legal category: P. **Package Quantities:** Containers of 100 capsules.
Basic NHS Cost: £15.98 (for 100 capsules). **Product Licence Number:** PL 76/129.

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Further information available from:
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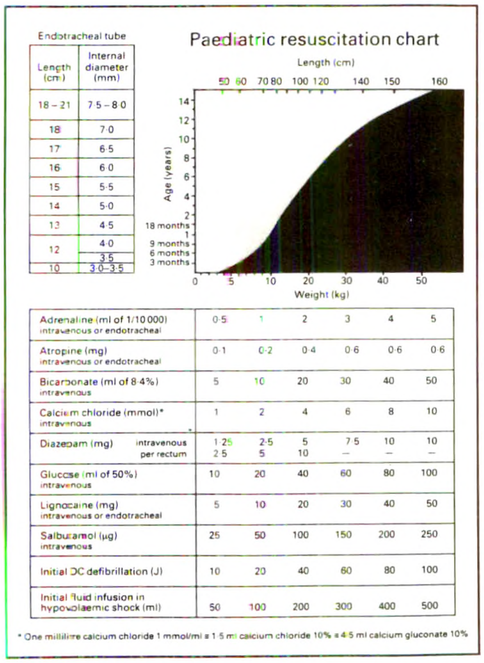
Enquiries may also be sent through BITNET to: **PERSDEPT @ NUSVM**



Paediatric resuscitation chart

Endotracheal tube

Length (cm)	Internal diameter (mm)
18 – 21	7·5 – 8·0
18	7·0
17	6·5
16	6·0
15	5·5
14	5·0
13	4·5
12	4·0
	3·5
10	3·0–3·5

Adrenaline (ml of 1/10 000) intravenous or endotracheal		0·5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal		0·1	0·2	0·4	0·6	0·6	0·6
Bicarbonate (ml of 8·4%) intravenous		5	10	20	30	40	50
Calcium chloride (mmol)* intravenous		1	2	4	6	8	10
Diazepam (mg)	intravenous	1·25	2·5	5	7·5	10	10
	per rectum	2·5	5	10	—	—	—
Glucose (ml of 50%) intravenous		10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal		5	10	20	30	40	50
Salbutamol (μg) intravenous		25	50	100	150	200	250
Initial DC defibrillation (J)		10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)		50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml ≡ 1·5 ml calcium chloride 10% ≡ 4·5 ml calcium gluconate 10%

A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

Poster: UK £3.50; Abroad £4.50; USA $9.00, including packing and postage, by air abroad.

Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.

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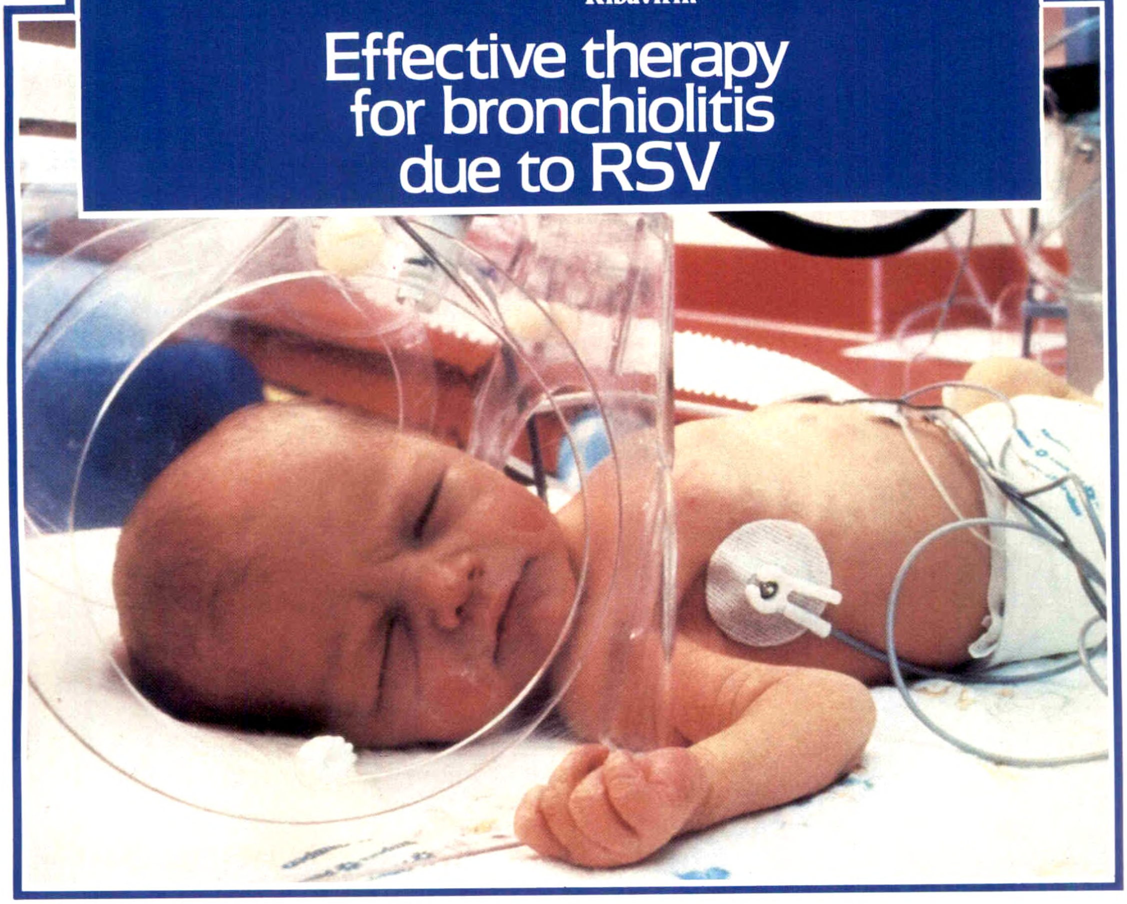

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Treatment is carried out using a small particle aerosol generator (SPAG) for 12-18 hours per day for at least 3 and no more than 7 days. The concentration of ribavirin in the reservoir is 20mg/ml in the SPAG unit and the average concentration for a 7 hour period is 0.19mg/l of air.

Presentation

Virazid is a sterile lyophilised powder of ribavirin to be reconstituted for aerosol administration. Each 100ml glass vial contains 6g of ribavirin and, when reconstituted to the correct volume of 300ml with Water for Injections BP, will contain 20mg/ml ribavirin at a pH of approximately 5.5.

Contra-Indications

Ribavirin is contra-indicated in females who are or may become pregnant and it should be noted that ribavirin can be detected in human blood even four weeks after oral administration has ceased.

Precautions

In infants requiring assisted ventilation, Virazid should only be used when there is constant monitoring of both patients and equipment.

Side Effects

Several serious adverse events occurred in severely ill infants with life-threatening underlying disease many of whom required assisted ventilation. These events included worsening of respiratory status, bacterial pneumonia and pneumothorax. The role of ribavirin aerosol in these events has not been determined.

Anaemia has been reported with oral and intravenous administration but no such incidents have been reported with aerosol administration. Reticulocytosis has been reported with aerosol use.

Warnings

Precipitation of the drug in respiratory equipment and consequent accumulation of fluid in the tubing has caused difficulties for patients requiring assisted ventilation.

In infants requiring assisted ventilation Virazid should only be used when there is constant monitoring of both patients and equipment.

Directions for use during assisted ventilation are given in the SPAG manual which should be read carefully before such administration.

Full prescribing information is available upon request.

▼Special reporting to the CSM required.

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Suspension comprising 30% Neutral Insulin Injection and 70% Isophane Insulin Injection (NPH), human insulin (emp)). HUMAN INITARD® 50/50 ▼ (Neutral Suspension comprising 50% Neutral Insulin Inject
and 50% Isophane Insulin Injection (NPH), human insulin (emp)). **Presentation** HUMAN VELOSULIN, HUMAN INSULATARD, HUMAN MIXTARD 30/70 and HUMAN INITARD 50/50 are availabl
10 ml. vials containing 100 iu/ml. To aid identification the metal sealing rings of the vials have tactile marks as follows: Human Velosulin – one mark; Human Insulatard – two marks; Human Mixtard 30/70 – th
marks; Human Initard 50/50 – four marks. The vials are fitted with tamper-evident caps. **Uses** The treatment of insulin-requiring diabetes. **Dosage and Administration** The dosage of insulin is determi
by the physician according to the needs of the patient. Human Velosulin may be given by s.c., i.m., or i.v. injection. Human Insulatard, Human Mixtard 30/70 and Human Initard 50/50 should be re-suspen
by inverting the vial several times before being given by s.c. or i.m. injection (they must not be given intravenously). Intermixing does not affect the characteristics of any of these insulins. **Use in pregnan**
Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. **Use in the elderly:** Insulin may have a more prolonged action due to reduced clearance ra
Contra-indications warnings etc. Contra-indications: Hypoglycaemia. **Precautions:** Patients transferring from other insulins may require a dosage adjustment. Concomitant therapy with thyrox
corticosteroids, oral contraceptives, diuretics, beta blockers and M.A.O.I.s may affect insulin requirements. **Side and Adverse Effects:** Hypoglycaemia. Local reactions, lipodystrophy and hypersensiti
reactions are rarely reported with human insulins. **Pharmaceutical Precautions** Store between 2–8°C, protected from sunlight. Insulin which has been frozen should
be used. **Legal Category** P. **Package Quantities** 10 ml. glass vials. **Basic NHS Price** £7.31. **Product Licence Numbers** NORDISK-UK: Human Velosulin 3132/00
Human Insulatard 3132/0034; Human Mixtard 30/70 3132/0037; Human Initard 50/50 3132/0040. THE WELLCOME FOUNDATION LTD: Human Velosulin 0003/0211; Hum
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Foundation Ltd, Crewe Hall, Crewe, Cheshire CW1 1UB. Tel: Crewe (0270) 583151. **Reference** 1. Heine R.J. et al, Diabetologia, 1984; 27; 558-562. ®Registered Trade M

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Archives of Disease in Childhood, 1988, **63,** 1301–1304

Annotations

Magnetic resonance in diseases of the nervous system

The anatomy and much of the pathology affecting the nervous system are well shown by the computer reconstructed sectional techniques of computed tomography and magnetic resonance imaging. The images from these techniques are quite similar and have common limitations of partial volume and reciprocation between contrast discrimination and spatial resolution, but the principles of their formation are radically different.

A computed tomogram is a sensitive measure of the linear absorption of x rays at all points within a selected section of the child to be studied. It is achieved by measuring the intensity of an incident and emergent beam, traversing the slice from multiple angles. Where the bone around the neuraxis is a fairly even plate excellent images are achieved. Differential absorption of x rays occurs, however, from the polychromatic beam where particularly dense bone surrounds the nervous system, and this is the basis of beam hardening artefacts, which detract considerably from the diagnostic value of computed tomography in the posterior and lower middle fossa, the spinal canal, and at craniocervical junction.

Certain nuclei behave like tiny bar magnets and when the body is placed in a strong static magnetic field they align along the force lines of the field and gyrate or precess around the axis of the field at a rate unique for type of nucleus, but within the radio frequency range and proportional to the strength of the field. By transmitting radio waves at the precession frequency the gyrating nuclei can be brought into phase and, at the same time, energy is added to the system. The synchronised nuclei emit a radio frequency signal that can be sufficiently strong to be recorded by a suitably placed receiving coil.

The most abundant nucleus in the body to behave in this way is the proton and it is the basis of all current magnetic resonance imaging. The superimposition on the static field of gradient fields allows precise localisation of the transmitting protons, their radio signals can therefore form the substrate of an image. Radio signals are free from the mechanical restraints which apply in computed tomography, so that magnetic resonance images can be obtained in any plane simply by modification of the direction of the gradient fields.

The image contrast is proportional to the strength of the signals at the time of imaging, which depends on.

(1) The density of the mobile protons in the tissue to be imaged. As cortical bone contains few mobile protons it produces neither signal nor image degradation, so that there are particular advantages in using magnetic resonance imaging as the primary mode of investigation in regions where beam hardening detracts from images produced on computed tomography.

(2) The capacity of the protons to retain the radio frequency energy. This is dependent on the physical state of the protons in the individual tissues. The energy is lost in two main ways. (a) By molecular collisions or thermal interactions. The time taken by the protons to magnetise in the strong magnetic field is a measure of this function. It is referred to as T_1 or spin lattice relaxation time. (b) By exchange of energy between the resonating protons. This causes dephasing at an exponential rate, referred to as T_2 or spin-spin relaxation time.

The importance of relaxation behaviour in formation of the image is evident from the fact that a 10% difference in tissue water concentrations can cause up to a 200% contrast difference, which accounts for the exquisite sensitivity of magnetic resonance imaging.

Other important factors influencing the image include:

(1) Mechanical movements of protons, as in blood flow and pulsation of the cerebrospinal fluid, between stimulation and recording of signal.

(2) Paramagnetic substances, which produce large local variations in the magnetic field; most typical examples are some of the naturally occurring iron compounds, including deoxyhaemoglobin, methaemoglobin, ferritin, and haemosiderin.

(3) Chemical shift. Protons in fat and water, being bound differently, resonate at slightly different frequencies so that images generated from them may not quite superimpose.

Judicious selection of sequence parameters for magnetic resonance can cause image brightness to reflect preferentially the influence of any one of these individual factors.

Advantages and limitations of magnetic resonance imaging

The lack of ionising radiation or, indeed, any other known biological hazard is of particular importance in young patients, especially if serial examinations are necessary. Sensitivity, freedom from bone induced artefact, and multiplanar imaging combine to make magnetic resonance imaging the optimum method of examining the nervous system. It has a few disadvantages in addition to the initial expense and limited accessibility Even though it is now possible to record diagnostic data within seconds rather than the many minutes that used to be needed,[1] heavy sedation or general anaesthesia is still necessary in about 15% of cases. Monitoring and life support apparatus compatible with the magnetic field and anaesthetic equipment free of ferromagnetic objects are available. Patients with electromagnetic or ferromagnetic implants, or metallic foreign bodies in sensitive situations, as near the eye, or aneurysms in or adjacent to the spinal cord or brainstem, cannot be placed within the magnet, whereas they can be examined by computed tomography.

Contrast enhancement

Gadolinium diethylenetriamine pentacetic acid (DTPA) shortens the T_1 relaxation time. With respect to the blood-brain barrier, it is similar to the iodine based contrast media used in computed tomography.[2] Gadolinium enhancement has similar importance, but it is more sensitive The sensitivity of magnetic resonance imaging reduces the necessity for a contrast agent in most cases, but it can be particularly useful in:

(1) The demonstration of (a) tumours strongly suspected clinically but invisible on unenhanced magnetic resonance imaging, such as small neuromas and metastases; (b) solid components within an extensive cystic or oedematous swelling, particularly in the spinal cord where exact localisation allows treatment or biopsy through a limited laminectomy[3]; and (c) selected cases of acute demyelination and small inflammatory foci and distinction from gliotic lesions.

(2) Reducing imaging time, particularly for volume acquisition.

No severe reactions to gadolinium DTPA have been recorded, and even minor hypersensitivity is very rare.[4] Gadolinium is only available for routine clinical use in Germany, but licence applications have been filed in other countries, including Britian.

Clinical applications

DEVELOPMENT AND MYELINATION

Not only are all malformations and neuronal migration abnormalities at least as clearly shown by magnetic resonance imaging as by computed tomography, in addition, the extent of myelination and the effects of disease processes on its progress can be recognised at an early stage For example, periventricular leucomalacia and haemorrhage from the germinal matrix in premature infants can be closely monitored and adverse effects of any complicating hydrocephalus on myelination can be finely judged, facilitating informed management.

INFLAMMATORY LESIONS

Lesions are usually visible in acute allergic encephalomyelitis,[5] and infective encephalitis often shows non-specific changes on magnetic resonance imaging when computed tomography is negative: magnetic resonance should be the primary investigation when these diseases are suspected In pyogenic and granulomatous inflammation, particularly in the supratentorial region, magnetic resonance imaging has little advantage over computed tomography; in granulomatous meningitis, enhancement in the basal cisterns is the important diagnostic feature and computed tomography is currently the modality of choice. Magnetic resonance shows plaques as regions of prolonged T_1 and T_2, most often in the deep cerebral white matter, in virtually all patients with established multiple sclerosis[6]; magnetic resonance imaging, though non-specific, may indicate the possibility of multiple sclerosis and repeat magnetic resonance imaging may show new plaques to support the diagnosis.

LEUCODYSTROPHIES AND INHERITED ERRORS OF METABOLISM

In leucodystrophies with abnormal computed tomography, magnetic resonance imaging reflects the distribution and often shows more extensive disease. Where family screening is to be undertaken, magnetic resonance is the procedure of choice. White matter abnormalities have been shown in two female carriers of Pelizaeus-Merzbacher disease,[7] and the possibility of detecting subclinical changes in the carriers of other recessive or sex linked white matter diseases requires studying. In our limited experience, cases of metachromatic leucodystrophy that are negative on computed tomography have not shown abnormality on magnetic resonance imaging.

In inherited disorders of metabolism magnetic resonance imaging shows brain damage more exactly and at an earlier stage than computed tomography. The distribution may suggest particular groups of diseases, but the signal changes are rarely specific. The susceptibility of the basal ganglia to anoxia, metabolic acidosis, mitochondrial cytopathy, and Leigh's disease, Wilson's disease, Hallovorden-Spatz disease, and choreoacanthocytosis will suggest appropriate investigations for elucidation Widened Virchow-Robin spaces, particularly in the peritrigonal regions, are common in the mucopolysaccharidoses, and infarcts and communicating hydrocephalus may complicate these diseases. Diffuse signal changes have been shown in the white matter in ceroid lipofuscinosis. in which computed tomography shows minor atrophy at most. Diffuse ischaemic changes or lacunar infarction, or both, are also shown at a relatively earlier stage in Anderson-Fabry disease.

STROKE

Ischaemia and infarction increase the water content of both grey and white matter, and produce high signal on T_2 weighted images, in concentrations many times less than detectable by computed tomography. The advantages of magnetic resonance imaging are accentuated in the posterior fossa; most brainstem infarcts are not shown by computed tomography.

The behaviour of haemorrhage on magnetic resonance imaging is complex. Acute haemorrhage, including subarachnoid haemorrhage, is well shown and easily interpreted on computed tomography. It will be evident on magnetic resonance imaging if reduction of T_2 is present due to the presence of deoxyhaemoglobin Subacute and chronic haemorrhages are clearly and specifically shown by magnetic resonance imaging.[8]

VASCULAR LESIONS

The vascular anatomy outlined by the negative signal of flowing blood can show aneurysms and angiomatous malformations. Signal change reflecting intraluminal thrombus allows the diagnosis of arterial and dural sinus occlusion with appropriate sequences.[9]

HEAD INJURY

Extracerebral haematomas and the extent of parenchymal damage are better shown by magnetic resonance imaging than computed tomography.[10] Nevertheless, computed tomography is easier to perform in the acute stages after injury and is currently the procedure of choice in identification of surgically significant intracranial haematomas Magnetic resonance imaging may be particularly important in the assessment of residual brain damage

INTRACRANIAL TUMOURS

The much greater sensitivity of magnetic resonance imaging, particularly in the posterior fossa and foramen magnum region, and the value of coronal and sagittal imaging in assessment of brain stem and juxtasellar regions applies to tumour detection and assessment. In optic glioma, for example, the lack of signal from the dense bone around the optic canal allows the full length of the optic nerve, in addition to the chiasm and proximal optic tracts, to be clearly shown. Multiplicity of lesions is more definitively established, and this may influence diagnostic possibilities in favour of metastases, lymphoma, or multifocal glioma. The distinction between tumour edge and oedema, of cystic from solid neoplasm, and of gliosis and fibrosis from neoplasia is no more accurate with magnetic resonance imaging than with computed tomography, and with similar contributions from contrast enhancement. The specificity of magnetic resonance imaging may be less than that of computed tomography in some cases, as, for example, in small craniopharyngiomas in which calcification may be a crucial diagnostic feature.

SPINAL IMAGING

The spinal cord and theca and the extrathecal segments of the nerve roots are well shown; the intrathecal nerve roots are more reliably shown on myelography or computed myelography.

All aspects of dysraphism—meningocoele, myelomeningocoele, lipomeningocoele, and diastematomyelia—are well shown. The site of the conus, cord tethering, the association of lipoma or dermoid, Chiari malformation or syringomyelia or other abnormality of the cord can all be determined. Arachnoid and neurenteric cysts expand the subarachnoid space and displace the neuraxis; their importance as compressing agents may be deduced from deformity induced on the cord. Ependymal cysts and dural ectasia may be recognised from the signal of their contents, being similar to that of cerebrospinal fluid.

Any cord swelling is evident, but distinction between cystic and solid intrinsic tumours, and even between tumours and acute demyelinating processes, may be impossible from consideration of the images alone.[11-13]

Cord compression and the nature of the compressing agent is usually demonstrated. The extent of extramedullary neoplasms or of stenosis of the spinal canal associated with bony dysplasias and metabolic diseases is shown and the dangers of spinal puncture are avoided.

Intramedullary angiomatous malformations are evident, but dural angiomas are not routinely shown.

Magnetic resonance imaging is the favoured examination for elucidation of both acute and insidious spinal cord syndromes Myelitis, in the absence of swelling, cannot be detected by any other study, and intrinsic cord damage from acute or chronic trauma is best shown by magnetic resonance imaging

Computed tomography does have some advantages. fractures, dislocations, and osteophytes are more clearly shown; after penetrating trauma the possibility of retained metal close to the cord should be considered before placing the child in a magnet.

Conclusion

Magnetic resonance is the optimal method for primary diagnosis of structural disease of the brain and spinal cord, with the possible exception of acute haemorrhage and diseases where calcification is important for specific diagnosis. Until magnetic resonance imaging is freely available, however, computed tomography will remain as the screening investigation, followed by magnetic resonance imaging when it is doubtful or normal in cases in which structural disease is probable. In cases that are positive on computed tomography magnetic resonance imaging is likely to add important data only when multiplanar imaging is a critical consideration. Future prospects include the clinical introduction of sodium imaging, which may be useful in assessment of malignancy[14] and in the management of oedema by assessment of osmolarity. Phosphorous spectroscopy has not yet shown a specific abnormality in most pathologies,[15] though a correlation with prognosis has been shown in perinatal ischaemia. Improvements in the resolution of the method and, in particular, the introduction of hydrogen spectroscopy, may produce more useful results, particularly in elucidation of metabolic abnormalities

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Archives of Disease in Childhood, 1988, **63,** 1305–1308

Management of croup

Those who turn to the current paediatric textbooks for guidance on the management of croup may be forgiven if they are confused by what they read. Mist treatment, oxygen tents, corticosteroids, nebulised adrenaline, antibiotics, sedatives, intravenous fluids, syrup of ipecacuanha (one drop per month of age up to 2 years)[1] and endotracheal intubation are advocated with enthusiasm or caution but with scant supportive evidence. Controversy about management is fuelled by serious methodological deficiencies in published studies and failure to define clearly the condition being studied.[2 3] To some authors, croup is synonymous with viral laryngotracheobronchitis, whereas others use the term to describe a symptom-complex which includes spasmodic croup, bacterial tracheitis, and acute epiglottitis, as well as laryngotracheobronchitis.

Definitions

Croup can be defined as an acute clinical syndrome with inspiratory stridor, a barking cough, hoarseness, and signs of respiratory distress due to varying degrees of laryngeal or tracheal obstruction. This definition embraces several distinct disorders with different underlying pathophysiological processes, different clinical courses, and different responses to treatment.

Acute laryngotracheobronchitis, the commonest form of croup, is most frequently caused by the parainfluenza, influenza, or respiratory syncytial viruses. The onset of barking cough, hoarseness, and stridor is usually preceded by rhinorrhoea, a sore throat, and mild fever for one or two days. The symptoms often begin, and are worse, at night but normally disappear after two to seven days. Many children have stridor with little or no respiratory difficulty but a few develop increasing tachycardia, tachypnoea, sternal and subcostal recession, and restlessness indicating severe upper airway obstruction. The intensity of the stridor, like that of wheeze in asthma, is a poor indicator of the severity of obstruction.[4]

Some children have repeated episodes of croup without fever or coryzal symptoms. Their symptoms are of sudden onset and at night, and often persist for only a few hours. The association of this *recurrent* or *spasmodic croup* with atopic disease and an abnormal response to inhaled histamine, suggest that hyperreactivity of the upper airway may be the underlying mechanism.[5 6]

Bacterial tracheitis, or pseudomembranous croup, is an uncommon but life threatening form of croup.[7 8] Infection of the tracheal mucosa with *Staphyloccus aureus,* streptococci, or *Haemophilus influenzae* results in copious purulent secretions and mucosal necrosis. The child appears toxic with a high fever and the signs of progressive upper airway obstruction. The croupy cough and absence of drooling help distinguish this condition from acute epiglottitis.

Acute epiglottitis shares many of the clinical features of croup but should be regarded as a separate entity. *Haemophilus influenzae* B is the causative pathogen in virtually all cases, but streptococci can occasionally give a similar clinical picture. Although epiglottitis is a far less common cause of upper airway obstruction than croup, particularly in infancy, it is important because without prompt recognition and appropriate treatment there is a high risk of death. Typically the child presents with a history of a few hours of an intensely painful throat and increasing difficulty in breathing He is unable to talk or drink and will be drooling saliva because swallowing is so painful. A high fever and pallor are present and there may be signs of poor peripheral circulation. Characteristically, the child prefers to sit upright rather than to lie down. General features of upper airway obstruction such as sternal retraction, tachycardia, and tachypnoea, are present and may worsen rapidly, particularly if the child is disturbed excessively. The stridor of epiglottitis is usually quieter and less harsh than that of croup. The absence of a croupy cough in any child with acute stridor and fever strongly suggests a diagnosis of epiglottitis.

Diphtheria, retropharyngeal abscess and laryngeal foreign body are uncommon causes of acute stridor but may be fatal if not recognised.

Treatment of croup

Accurate diagnosis, gentle handling, and careful observation are the mainstays of good management. As the distinction between viral laryngotracheobronchitis and recurrent croup, which together account for most cases of croup, is often not made in clinical practice or in published reports, the management of these two disorders will be considered together. The treatment of bacterial tracheitis is described separately.

The diagnosis and assessment of the severity of croup are based on the history and clinical examination. Investigations such as the white cell count and microbiological cultures rarely influence management and should not be performed as a routine. Lateral radiographs of the neck are not a reliable indicator of the severity of airway obstruction [9] The procedure is disturbing to the child and can precipitate acute obstruction and therefore should be avoided.

GENERAL SUPPORTIVE MEASURES

Children with croup are often frightened, miserable, and uncomfortable. Crying increases their oxygen demand, accelerates respiratory muscle fatigue, and may increase laryngeal swelling. Gentle confident handling helps reassure the child (and parents). Children are often more peaceful on their mother's lap than in a strange cot. Occasionally a sedative such as chloral hydrate may be needed if the child remains agitated, but drugs that can cause repiratory depression must be avoided. Nursing and medical staff must recognise that restlessness and agitation may indicate serious hypoxaemia and not simply anxiety. Adequate hydration can usually be achieved by encouraging small frequent drinks. Children with severe dyspnoea may need intravenous fluids. Nasogastric tubes cause discomfort and increase respiratory distress, and should be avoided.

MIST TREATMENT

Warm mist or water vapour is still used in the treatment of croup. In hospital, humidifiers or nebulisers are used to increase the water content of air or oxygen, which may be delivered into a plastic tent or via a face mask held a few inches from the child's mouth. Mist tents are uncomfortable and can be frightening, and they make observation more difficult. Although there is anecdotal support for the use of mist in croup, there is no objective evidence of benefit and it is unclear how mist might reduce respiratory obstruction. Bourchier and colleagues showed no significant differences over a 12 hour period in the physical signs or transcutaneous oxygen and carbon dioxide concentrations between two groups of children with viral croup, who were randomly allocated to high or normal humidity.[10] The small numbers of patients (eight in each group), however, and the wide variance of most of the parameters measured, precludes a firm conclusion about this negative result. There are no other controlled studies of humidity in croup.

OXYGEN

Hypoxaemia, due to impaired alveolar ventilation and ventilation-perfusion imbalance, is common in children admitted with croup.[11] The degree of hypoxaemia correlates poorly with clinical signs: the respiratory rate is the best indicator of a lowered arterial oxygen tension. Although oxygen treatment may delay the appearance of cyanosis and agitation due to hypoxia, other clinical signs such as increasing sternal retraction, tachypnoea, and tachycardia are not alleviated by oxygen and allow recognition of increasing obstruction. The measurement of oxygen saturation with pulse oximetry may be a valuable adjunct to clinical assessment. Not all croupy children admitted to hospital need oxygen but it may help those with moderate or pronounced dyspnoea. It is difficult to achieve an oxygen concentration above 40% in a tent and few children will tolerate face masks. They may, however, accept a mask which is held a short distance above their face, but the efficacy of this method of delivering oxygen is uncertain.

NEBULISED ADRENALINE

In 1971, Adair *et al* reported 10 years' experience of the use of racemic adrenaline delivered by intermittent positive pressure breathing in 550 children with laryngotracheobronchitis.[12] (Racemic adrenaline is an equal mixture of the L- and R- isomers, but L-adrenaline is the active component.) Adair claimed that this treatment improved airway patency and reduced or abolished the need for tracheostomy or intubation. Several small prospective controlled studies have failed to confirm Adair's retrospective observations. Although inhalation of nebulised racemic adrenaline produced improvement of clinical signs[13–16] and a fall in respiratory resistance,[14] these effects were shortlived (30–60 minutes) and were not associated with improvement in arterial blood gas tensions.[13] A similar change occurred when adrenaline was delivered by simple nebulisation without intermittent positive pressure breathing.[15] The duration of hospitalisation and the need for an artificial airway were not reduced in these studies.

Racemic adrenaline is not available in this country but adrenaline 1:1000 BP is equally effective.[16] The dose of 5 ml, delivered from a nebuliser via face mask, can be repeated every two to four hours. Significant side effects have not been reported but all children receiving the drug need careful observation, preferably in an intensive care unit with continuous electrocardiographic monitoring. This form of treatment should be reserved for children with severe obstruction. Children who have no improvement or who require repeated inhalations are likely to require intubation. The transient improvement may be of value in the child who needs endotracheal intubation, while waiting for an experienced anaesthetist.

STEROIDS

Over the last 20 years there have been more studies to evaluate the role of corticosteroids in the management of croup than any other form of treatment. The results of these trials are confusing and conflicting because of major faults in their design [2 3 17] In some studies there was no distinction between viral laryngotracheobronchitis and spasmodic croup, and often no allowance for the severity of the illness. Random assignment to treatment or non-treatment groups and double blind techniques were not always employed. Different steroids have been given in different doses by different routes. Patients usually received several other treatments, such as mist or adrenaline, concurrently with steroids. There have been no agreed criteria for assessing the effects of treatment These deficiencies make interpretation of the reported data impossible. It is difficult to justify the use of corticosteroids for a condition that almost always resolves without any specific treatment

ENDOTRACHEAL INTUBATION

About 2–5% of children admitted with croup require an artificial airway [18] The decision to intubate is a clinical one based on increasing tachycardia, tachypnoea, and chest retraction, or the appearance of cyanosis, exhaustion, or confusion. The procedure should be performed under general anaesthetic by an experienced anaesthetist, except where there has been a respiratory arrest If there is doubt about the diagnosis, an ear, nose, and throat surgeon capable of performing a tracheostomy should be present. Anaesthetic induction should be with oxygen and halothane through a face mask. Intravenous induction agents and relaxants should not be used Many anaesthetists pass an orotracheal tube initially and then exchange this for a nasotracheal tube after adequate oxygenation and thorough tracheal suction have been achieved. Pulmonary oedema and pneumothorax or pneumomediastinum are uncommon complications.

Children with an endotracheal tube need meticulous observation in an intensive care unit if potentially fatal complications such as tube blockage or displacement are to be avoided. Thorough humidification of inspired gases using the humidifier of a ventilator circuit, and careful tracheal suction are essential to prevent concretion of secretions and tube blockage. Secondary infection with staphylococcus and haemophilus is common and may require appropriate antibiotics The median duration of intubation in croup is four to five days. Nebulised adrenaline may reduce the stridor which follows extubation [18] Although tracheostomy is an equally effective way of alleviating obstruction, the morbidity and mortality are higher than with intubation. Tracheostomy should be reserved for the small minority of children where endotracheal intubation cannot be achieved, where there is recurrent tube blockage, or where prolonged intubation runs the risk of subglottic scarring.

Management of bacterial tracheitis

Early diagnosis and treatment of this potentially fatal infection are essential as the management is very different from that of other forms of croup. Four fifths of children in reported series have required intubation for severe tracheal obstruction.[7 8] At intubation, pus aspirated from the trachea should be sent for bacterial culture. Blood cultures should also be taken, although bacteraemia is uncommon Intravenous ampicillin and flucloxacillin should be given for seven to 10 days unless the results of bacterial culture indicate the use of other antibiotics. Even with frequent endotracheal suction and careful humidification, blockage of the endotracheal tube by crusted secretions can occur and tracheostomy may be required. There is no evidence that nebulised adrenaline or steroids are of benefit in bacterial tracheitis

Conclusions

With the exception of antibiotics in bacterial tracheitis, there is no convincing evidence that any drug alters the natural history of croup. The brief duration of the improvement produced in some patients by nebulised adrenaline severely limits its clinical value. Steroid and mist treatment cannot be recommended on the basis of available data Oxygen is almost certainly underused and saturation monitors may be helpful in assessing the need for oxygen.

In most children, croup is a self limiting disease requiring only considerate handling, but in a minority there is life threatening airways obstruction Deaths from croup still occur. Some of these deaths could be avoided by more careful diagnosis of the cause of the upper airway obstruction, by earlier recognition of the clinical signs of severe obstruction and hypoxaemia, and by more prompt relief of severe obstruction by intubation. The crucial aspect of the efficient management of croup is the early recognition and alleviation of impending total respiratory obstruction.

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Archives of Disease in Childhood, 1988, **63,** 1309–1314

Renal parenchymal volume during and after acute pyelonephritis measured by ultrasonography

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SUMMARY A total of 47 children with acute pyelonephritis were investigated using water delay ultrasonographic equipment (Octoson) for determination of renal parenchymal volume by the stepped section technique. Thirty two patients were repeatedly investigated every to every other week up to seven weeks. Median renal parenchymal volume during acute pyelonephritis of the right kidney was 2·70 cm^3/kg body weight and of the left kidney 3·10 cm^3/kg; this was significantly larger than the volume of control kidneys, which was 1·82 and 2·07 cm^3/kg, respectively. The most enlarged kidneys were found among the youngest children. A significant successive decrease in renal size was found during the first four to five weeks after the acute pyelonephritis.

Because of enlargement of the kidneys during acute pyelonephritis we suggest that the first renal size determination to be used for following renal growth should be performed after at least four to six weeks.

Three per cent of all girls will contract a symptomatic urinary tract infection before the age of 11.[1] Half of them will have recurrent infections and 4·5–13% will develop renal scarring, with or without concomitant vesicoureteric reflux.[1 2] Cessation of renal growth after upper urinary tract infection—that is, acute pyelonephritis—has also been described.[3–6] Consequently most children in Sweden have, so far, been investigated radiologically employing urography and micturition cystography after their first infection of acute pyelonephritis. Follow up urography has been performed about two years later to determine renal growth and to detect possible renal scarring. Renal scarring can also be detected by scanning with technetium labelled dimercaptosuccinic acid (^{99m}Tc DMSA).[7]

Renal enlargement has been described in adults with acute severe suppurative pyelonephritis,[8–11] while in children with even less severe acute pyelonephritis renal enlargement seems to occur more often.[12 13] Renal size had decreased about two months after the acute infection.[12] The exact time for the regression of this enlargement has not been clarified. It is now possible to perform repeated ultrasonographic investigations at short intervals and thereby determine more precisely the point in time of this regression.

The aim of the present investigation was to determine accurately the renal parenchymal volume by ultrasonography during the acute phase of the pyelonephritic infection and to follow up the change in renal parenchymal volume in children. We considered it essential to determine the time at which the renal enlargement had regressed in order to find the optimal time for the first examination of renal size after acute pyelonephritis. If this examination is performed too early the kidneys are still enlarged. The overestimation of renal size during the acute infection might later lead to an erroneous interpretation of retarded renal growth at the second renal size determination.

Patients and methods

A total of 47 children, aged 0·4–15·4 years (median 4·3), were investigated. They all fulfilled the essential criteria for acute pyelonephritis as established by Jodal *et al.*[14] All children had symptoms of fever with a temperature of more than 38·5°C, a raised erythrocyte sedimentation rate of >20 mm in the first hour or a raised C reactive protein concentration (>10 mg/l), or both, as well as leucocyturia and positive urine cultures with a bacterial count of >100 000/ml of a single species or >1000/ml in urine from suprapubic aspiration. All children were admitted to hospital and antibacterial treatment was started immediately after blood and urine specimens had been taken. The first ultrasonographic examination was performed in all 47 children within the first week of admission It was intended that the ultrasonography be repeated every to every other week up to about seven weeks. Some patients could not come to the hospital so often, some parents refused to come, and we also experienced technical faults with the ultrasonographic equipment; this resulted in 32 children being investigated two to five times (mean three) during the first seven weeks.

The ultrasonographic examination was carried out with automated water delay ultrasonographic equipment, the Octoson (Ausonics Ltd), and the renal parenchymal volume was determined by the stepped section method with longitudinal scans taken at 0·5 cm intervals [15] The volume of the renal parenchyma was calculated on the basis of the parenchymal areas of each scan multiplied by the thickness of the scans To be able to compare renal sizes of children of different ages we have related our values to body weight.[16]

The method of measuring renal parenchymal volume had a methodological error of 0·16 cm^3/kg for the right kidney and 0·14 cm^3/kg for the left kidney. Kidneys showing a change in renal parenchymal volume >0·3 cm^3/kg between the acute examination and that performed after three to six weeks were considered to be affected by the infection.

Mann-Whitney's test and the paired *t* test were used for statistical analysis. Results of 43 control subjects from a previous study were used for comparison.[16]

Results

Fig 1 shows one girl who first presented with a lower urinary tract infection after which she was investigated ultrasonographically Two days later she became ill with acute pyelonephritis and new ultrasonography was done. The renal parenchymal volume of the left kidney increased from 43 cm^3 to 59 cm^3 (137% of initial volume) and the right from 49 cm^3 to 67 cm^3 (137%). The enlargement seems to have remained unchanged for a week, after which a gradual decrease in size was seen, reaching the initial value about four weeks later.

Fig 2 shows the renal parenchymal volume of the right and left kidney during the acute phase of acute pyelonephritis and the corresponding parenchymal volumes in the control series.[16] As it is clinically impossible to know whether acute pyelonephritis is unilateral or bilateral, especially in small children, we have decided to show the sizes of all kidneys irrespective of whether they are infected or not. The median renal parenchymal volumes of the right and left kidney at infection were 2·70 and 3·10 cm^3/kg

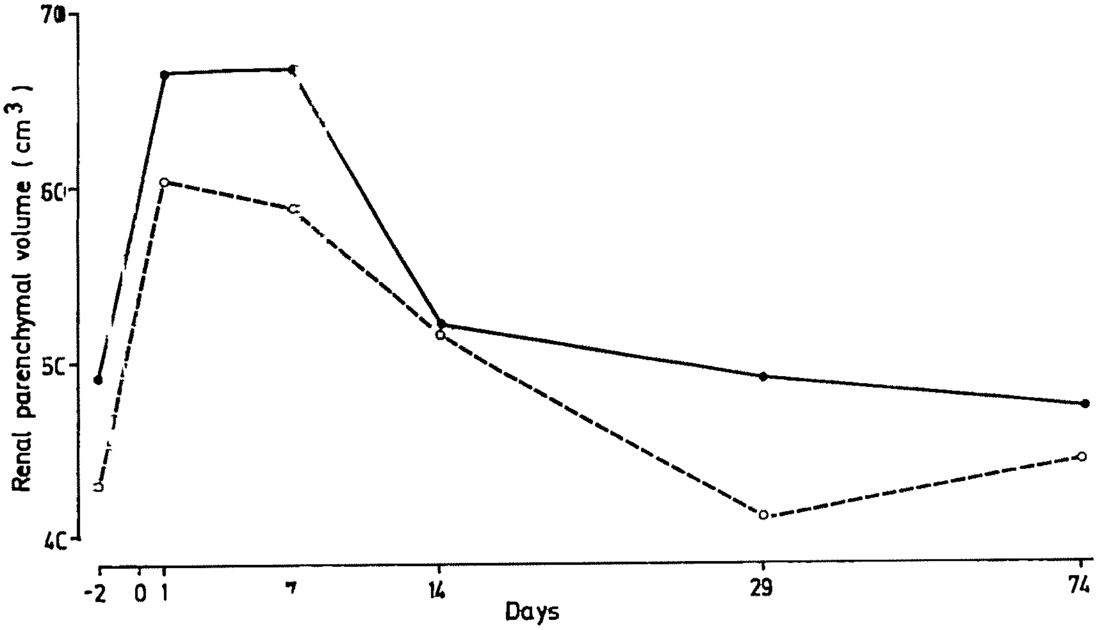

Fig 1 *Renal parenchymal volume of the right (unbroken line) and left (broken line) kidney of a girl examined two days before and at one, seven, 14, 29, and 74 days after acute pyelonephritis.*

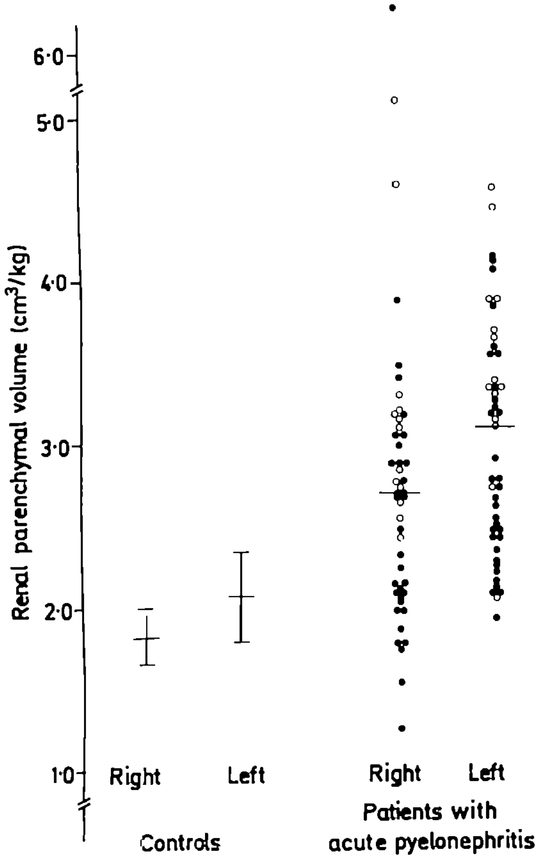

Fig 2 *Renal parenchymal volume, expressed in* cm^3/kg *body weight, of the right and left kidney in 47 children with acute pyelonephritis Median values are indicated by straight lines.* O=*Children* ≤*2 years;* ●=*children* >*2 years of age. As a comparison the median values as well as the 25th and 75th percentiles of the right and left kidneys from 43 controls are given.*[16]

body weight (range 1·25–6·26 and 1·92–4·56 cm^3/kg, respectively). This was significantly higher than those of the control kidneys with a median value for the right kidney of 1·82 and for the left kidney of 2·07 cm^3/kg body weight (mean (SD) 1·83 (0·27) and 2·10 (0·34) cm^3/kg, respectively). Thirty (64%) of the right kidneys and 26 (55%) of the left kidneys of patients with acute pyelonephritis were so enlarged that they were above +2SD of the sizes in controls. To clarify whether there was an age difference in patients with more or less enlarged kidneys the 47 patients with acute pyelonephritis were stratified into three groups: (1) those with both renal parenchymal volumes >+2SD of that of controls (n=20); their median age was 1·3 years) (2) those with one renal parenchymal volume >+2SD of that of controls (n=18); their median age was 4·7 years, and (3) those with both renal parenchymal volumes <+2SD of that of controls (n=9); their median age was 8 years. The difference between group (1) and (2) and between (2) and (3) was significant: $p<0·01$ and $p<0·05$, respectively. In the youngest patients both kidneys were often enlarged >+2SD while so pronounced an enlargement was less frequent in the older children.

Fig 3 shows changes in renal parenchymal volume from the first week to the third to sixth week in 30 patients studied on these two occasions. Patients are divided into those in whom both kidneys decreased >0·3 cm^3/kg, assessed as bilateral acute pyelonephritis (n=20) and those with only one kidney changing >0·3 cm^3/kg, assessed as unilateral acute pyelonephritis (n=10). The median decrease in the most affected kidney with bilateral acute pyelonephritis was 1·20 cm^3/kg while that of the least affected kidney was 0·74 cm^3/kg. In those patients with an assumed unilateral acute pyelonephritis the median decrease was 0·70 cm^3/kg and the mean decrease in volume of all affected kidneys was 0·87 cm^3/kg body weight.

Fig 4 a and b and the table show the changes in renal parenchymal volume of the right and left kidney of 32 patients during the first seven weeks after starting antibiotic treatment. The figures indicate the significant changes in renal parenchymal volume determined by the paired *t* test. When all kidneys were compared (right+left), there was a significant decrease in renal parenchymal volume from the periods one to eight days to nine to 16 days ($p<0·001$, paired *t* test) No significant change was found between the periods nine to 16 days and 17 to 24 days but there was a significant decrease between the period nine to 16 days and 25 to 32 days or 33 to 49 days ($p<0·01$ and $p<0·001$, respectively). No significant change was found between the periods 17 to 24 days, 25 to 32 days, and 33 to 49 days. When these last three periods were combined—that is, 17 to 49 days—there was a significant fall in renal parenchymal volume from nine to 16 days to 17 to 49 days (compared by the paired *t* test). Thus the renal parenchymal volume decreased during the first three to four weeks after acute pyelonephritis; thereafter no significant change was seen.

Discussion

The most commonly described sonographic sign of acute pyelonephritis, except enlargement, is decreased echogenicity in the corticomedullary region.[17–19] We could not confirm this by our method in conformity with Dinkel *et al*,[13] who consider sonolucency a variable sign, dependent on subjective judgment and therefore unreliable. We,

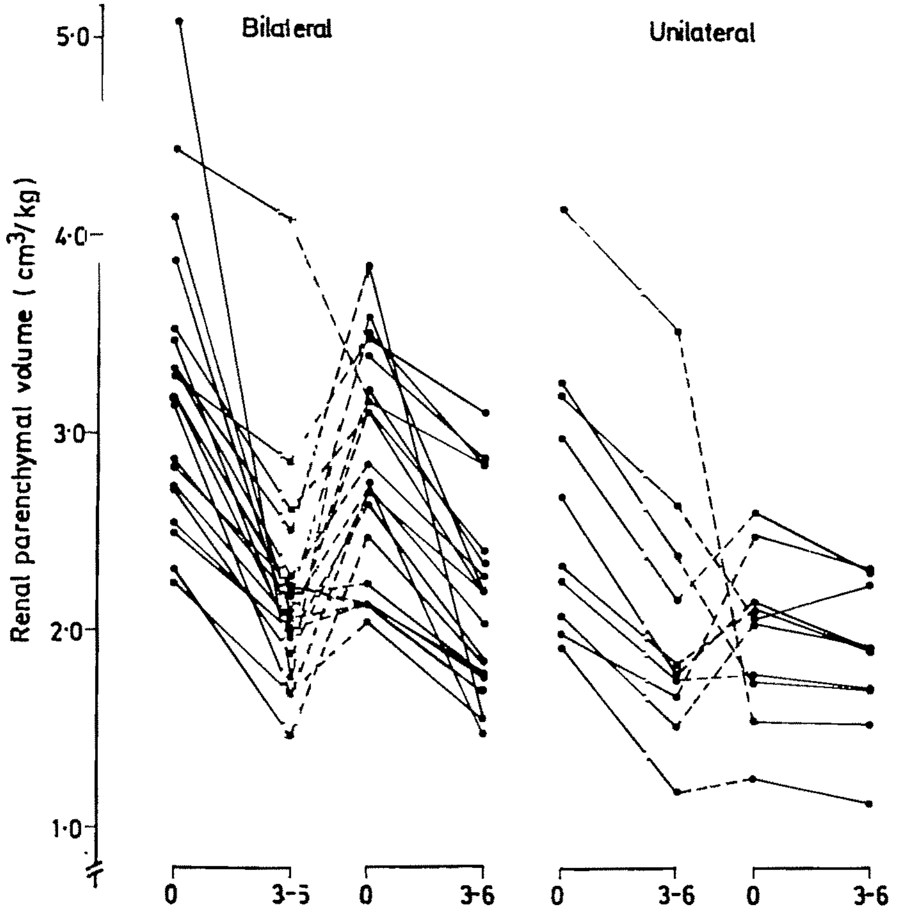

Fig 3 *Renal parenchymal volume (cm^3/kg body weight) in 30 patients, examined during the first week acute pyelonephritis and three to six weeks after, and assessed as bilateral and unilateral acute pyelonephritis The volume of the most affected kidney (that is, with the greatest change in renal parenchymal volume) is drawn to the left. The broken lines combine the two kidneys of each patient*

like them, found an increased kidney size. Their determination of kidney volume is based on formula for the ellipsoid using length, width, and depth,[20] and is thus quite different from our stepped section method. Dinkel *et al* found in acute pyelonephritis an average kidney volume of 175% of normal, while we found a renal parenchymal volume of about 150%. This difference might be explained by the different methods used. Dinkel *et al* include the renal pelvis in their measurements but they claim that the increased kidney volume is caused primarily by parenchymal thickening. Provided that the total kidney volume of Dinkel *et al* of 175% is a correct and reliable measurement, our calculation of the parenchyma volume as 150% must imply that the renal pelvis and the central high echogenic structures also increase in size during acute pyelonephritis. This is in accord with several authors who describe the dilated collecting system secondary to paralysis of the ureter as a consequence of bacterial endotoxins.[8 21–23] Furthermore, we performed our ultrasound examinations as soon as possible but sometimes a delay of a few days was inevitable and treatment was started. The regression in kidney volume could have started then.

We have chosen to determine renal size by renal parenchymal volume instead of just measuring renal length. Volume measurements, if accurate, are more sensitive to changes in renal size than single measurements of length. A change in kidney size

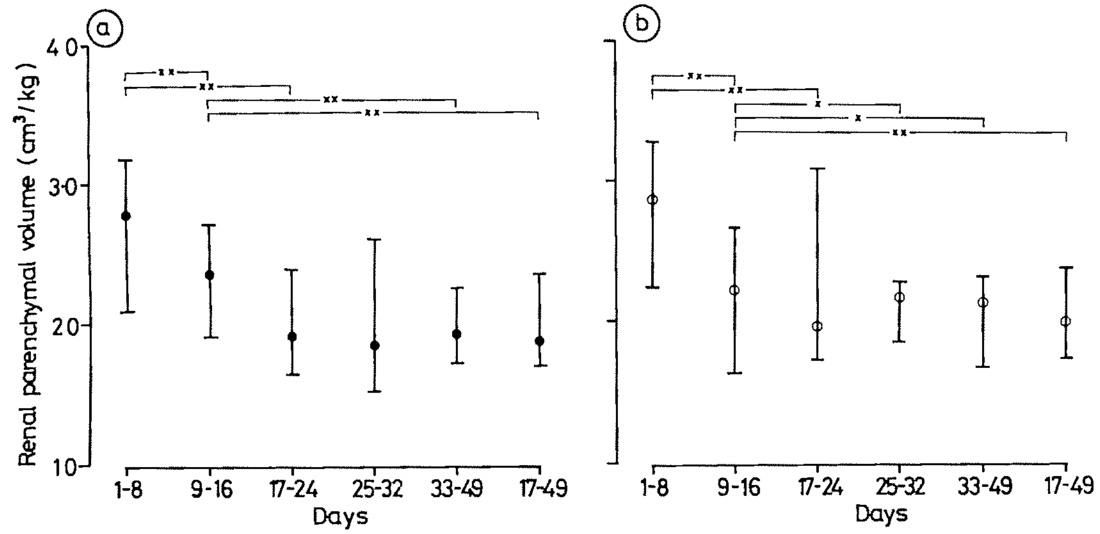

Fig 4a and b *Median values of renal parenchymal volume as well as the 25th and 75th percentile of the right and the left kidney of 32 patients examined repeatedly. Significant changes, calculated by paired t test, are indicated in the figure* *x=$p<0·05$, xx=$p<0·01$ ●=Right kidney (a); ○=left kidney (b).*

Table *Mean and median renal parenchymal volumes of the two kidneys after different periods of time after acute pyelonephritis*

	Time after start of antibiotic treatment (days)					*Controls (n=43)*
	1–8 (n=30)	*9–16 (n=18)*	*17–24 (n=16)*	*25–32 (n=12)*	*33–49 (n=18)*	
Right kidney:						
Mean	2·71	2·27	2·07	1·98	2·05	1·83
Median	2·78	2·36	1·89	1·86	1·94	1·82
Left kidney:						
Mean	2·93	2·30	2·44	2·25	2·11	2·10
Median	2·92	2·28	2·03	2·24	2·21	2·07

that is reflected by a change in length of 12% can be suspected to be due to a methodological error. An increase in all diameters of the kidney by 12% is equivalent to an increase in volume of 40%, which cannot be attributed to a methodological error.

The increased renal parenchymal volume found in this study might be due to oedema of the infected kidney according to Heptinstall,[24] but it might also be caused by hyperaemia secondary to an increased renal plasma flow found in acute pyelonephritis.[25] Whether or not the rapid decline in size seen during the first two weeks is caused by a regression of oedema or hyperaemia, or both, remains to be elucidated.

The most enlarged kidneys were found among the smallest children, which is in accord with Dinkel *et al.*[13] We also found that infants and small children had bilateral infections more often. This confirms a previous study performed in children with recurrent urinary tract infection after acute pyelonephritis in which we reported that only children having had their first infection with acute pyelonephritis before the age of 3 years had reduced glomerular filtration rates.[26] This, we thought, was due to the fact that small children more often had bilateral infections with a poor capacity for compensatory hypertrophy in previously infected kidneys.[26]

The enlargement of the kidneys during the acute phase of the infection regressed within four weeks. The most prominent decrease in renal size was found during the first two weeks. No clear cut decrease was found from the second to the third week but there was one from the second to the fourth or fifth week. Dinkel *et al* concluded that there was a nearly complete normalisation of kidney volume after four to six days, but in their results they reported a reduction in kidney volume of 20–45% within six to eight days and of up to 60% within two weeks.[13] It is somewhat difficult to determine from their presentation the exact time when the size of the kidney returned to normal.

In conclusion, the parenchymal volume in kidneys affected by acute pyelonephritis increases to around 150%. This enlargement regresses within four to five weeks. We therefore suggest that the first examination for determination of renal size, urography, or ultrasonography after acute pyelonephritis should be performed after at least four to six weeks. An early ultrasonographic examination is recommended, however, to exclude obstructive uropathy as well as for level diagnosis of urinary tract infection as an enlarged kidney is a sign of upper urinary tract infection.

This study was supported by grants from the Karolinska Institute and the Swedish Medical Research Council (No 06864)

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Accepted 30 March 1988

Archives of Disease in Childhood, 1988, **63,** 1315–1319

^{99m}Tc dimercaptosuccinic acid (DMSA) scan in patients with established radiological renal scarring

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SUMMARY The findings on ^{99m}Tc dimercaptosuccinic acid (DMSA) scans were examined in 54 patients aged 3 to 33 years in whom renal scarring had been diagnosed radiologically in childhood after urinary tract infection. There was no recent history of infection. Vesicoureteric reflux had been present in 48 patients and had stopped in 23 at the time of the DMSA scan. In six of the 72 radiologically scarred kidneys, the DMSA scan appeared normal but scarring would have been overlooked in only two of the 54 patients. DMSA scan changes are non-specific and underestimated individual scars in 21 kidneys. The intravenous urogram and the DMSA scan showed good correlation but should be regarded as complementary investigations in these patients, giving morphological and functional information, respectively. On DMSA scans the timing of any preceding urinary tract infection must be considered in order to differentiate diffuse potentially reversible defects in isotope uptake after urinary tract infection from those due to permanent renal scarring.

New imaging techniques have been introduced for the investigation of the urinary tract that are less invasive or give less radiation exposure than the established radiological methods. There has been limited parallel evaluation, however, at a time when the new methods are evolving and experience and expertise in their use is being gained.

The radiological features that identify the coarse renal scarring of chronic atrophic pyelonephritis or reflux nephropathy are long established.[1] They include deformity or clubbing of the calyx with thinning of the overlying parenchyma, distributed irregularly through the kidney and particularly affecting the renal poles. When scarring is segmental and not generalised, hypertrophy of the intervening normal tissue produces an irregular renal outline. The overall renal size is usually reduced. These changes correspond closely to the morbid anatomy of the condition. The value of the ^{99m}Tc dimercaptosuccinic acid (DMSA) scan in these patients has been clearly shown: areas of impaired DMSA uptake may indicate a segmental scar.[2-6] In some of these studies, however, the effects of recent infection have not always been excluded.

After noting a number of discrepancies between the radiological and DMSA scan reports in patients with established renal scarring on intravenous urography, we undertook a study of the DMSA scan findings in a group of such patients in whom there was no recent history of urinary infection.

Patients and methods

We studied 54 patients (10 males, 44 females) who ranged in age from 3 to 33 years. They originally presented with urinary tract infection aged 1 month to 12 years in the paediatric department, University College Hospital, and were found to have chronic atrophic pyelonephritis on intravenous urography. Subsequently all but three had serial follow up films confirming the renal scarring. A micturating cystourethrogram was also carried out in each child.

All the patients were maintained on low dose antibacterial prophylaxis until mid adolescence and were followed up with urine culture, blood pressure, and height measurements at three month intervals; this extended after the age of 15 to six or 12 month intervals. Limited serial radiological investigation was performed every two to three years during the growing years. Patients with outflow obstruction, stones, or complex renal anomalies, including horseshoe kidneys, were excluded from this study.

Renal scarring was bilateral in 18 and unilateral in 36, making a total of 72 scarred kidneys: 42 right and 30 left. There were seven duplex kidneys, five of them scarred, in five patients. Vesicoureteric reflux was seen in the ureter draining the scarred kidney in 50 patients (67 kidneys) and was presumed to have ceased in four in whom the micturating cystogram had been delayed until over the age of 12 years. In 34 of the 67 kidneys, reflux was severe with dilatation of ureter and renal pelvis. At the time of the DMSA scan, vesicoureteric reflux was known to have ceased in 30 patients, and in 44 ureters draining scarred kidneys. In seven patients (12 ureters) it was corrected surgically and in 23 patients (32 ureters) it stopped spontaneously. Reflux occurred initially into 16 radiologically normal kidneys and had ceased spontaneously in nine.

Three patients had intermittent hypertension and two others were on hypotensive drugs. Plasma creatinine concentrations were in the normal range for age in all patients, but at the upper limit in two. Symptomatic urinary infection had not occurred for at least three months before any of the investigations.

Standard intravenous urograms were taken on the subjects as outpatients. Conray 280 was used for young children and Conray 420 for older children until 1985 when these were replaced by non-ionic contrast media. Since then iohexol 240 or 300 at 2·5 ml/kg for children under 1 year, and iohexol 300 at 2·5–3 ml/kg (up to a maximum of 40 ml) has been used. An initial four film intravenous urogram was carried out over 30 minutes. Follow up at intervals of not less than two years was limited to a single 12 minute film of the renal areas. Tomography was occasionally needed in the youngest children.

The extent and distribution of scarring on intravenous urography were described as follows: *group 1:* one or two polar scars, or a laterally placed scar, or a polar and laterally placed scar; *group 2:* three or more focal scars (multiple); and *group 3:* a uniformly shrunken or globally scarred kidney.

The ^{99m}Tc DMSA scan was performed using an IGE—400T Gamma camera until 1985 when this was replaced by an IGE 400AC Starcam Anga Gamma camera. Posterior and both oblique views were routinely performed four hours after injection of the dose, which was adjusted to the child's body weight and based on a standard adult dose of 150 MBq. In most patients a renogram using ^{99m}Tc diethylenetriamine pentacetic acid (DTPA) was carried out either in combination with the DMSA or on a separate occasion, to exclude obstruction at the vesicoureteric or pelviureteric junction and to measure the proportionate function of each kidney.[7]

The interval between the intravenous urogram and DMSA scan varied but, apart from the adults without recurrent urinary tract infection in whom the findings on intravenous urography had already been shown to be constant, it did not exceed two years and in the younger children was usually less than three months. The intravenous urogram showing established scarring always preceded the DMSA scan.

The DMSA scans and the intravenous urograms were reviewed individually and blind in each patient. The results were then compared for each kidney and each child both for abnormality and morphological detail. The independent routine reports of the intravenous urogram and DMSA scan were also compared.

Results

REVIEW OF INTRAVENOUS UROGRAMS AND DMSA SCANS FOR RENAL ABNORMALITY

There was good correlation of renal abnormality in 48 of the 54 patients (89%) and in 66 of the 72 radiologically scarred kidneys (92%). In six kidneys, however, no abnormality was reported or noted on review of the DMSA scan. These occurred in six girls, in three of whom radiological scarring was bilateral. The scars that were not recognised on the DMSA scan were localised to the poles in five; four were left kidneys and three kidneys had more than one scar. Although three of the patients had unilateral scarring, this would have been missed in only two patients as the contralateral kidney was reported to be abnormal on the DMSA scan in one of them and further investigation would have followed. The distribution of function between the kidneys in these patients estimated by DTPA and DMSA renography was not helpful as in only one patient, with unilateral scarring, did it differ by more than 10%.

Among 36 patients with unilateral scarring, the DMSA scan suggested an abnormality of three contralateral, radiologically normal, kidneys. On review, two of these appeared to be due to a splenic impression. The third is under continued observation.

DETAILED COMPARISON OF INTRAVENOUS UROGRAMS AND DMSA SCANS

(1) Morphology (table)

In group 1 scarring was confined to one or both poles in 19 kidneys and to the lateral mid zone in two. Eight kidneys had both a polar and a mid zone scar. These three patterns of scarring were considered together. All six disparate kidneys were in this group. The three kidneys that appeared to be small with a smooth outline and without focal defects on the DMSA scan each had bipolar scarring.

There was very close correlation in the interpretation of the appearances on the intravenous urogram

Table *Review of the renal findings on the DMSA scan in 54 patients with 72 radiologically scarred kidneys, 42 right and 30 left*

Extent of renal scarring on intravenous urography	*Renal appearance on DMSA scan*						*Renal appearance on the DMSA scan compared with intravenous urogram*			*Total No of scarred kidneys on intravenous urography (right)*
	Small	*Small with focal defects*		*Focal defects*		*Normal*	*Correlation*	*Underestimate†*	*Disagreement‡*	
		*Correlation**	*Underestimate†*	*Correlation**	*Underestimate†*					
Group 1 1 or 2 polar or mid zone	3	1	1	11	7	6	15	8	6	29 (16)
Group 2 Multiple (≥ 3 scars)	3	5	4	4	9		12	13		25 (12)
Group 3 Global	3	10					18			18 (14)
Totals	14	21		31		6	45	21	6	72 (42)

*=Abnormality on DMSA scan correlating with radiological scarring, †=underestimate of scarred areas, and ‡=disagreement between the findings on the DMSA scan and intravenous urogram

and DMSA scan in all the kidneys with severe and fairly generalised scarring (group 3). In group 2, 25 kidneys had several scars and multiple focal defects were noted on the DMSA scan in 22 of them. The DMSA scan, however, underestimated the number of scarred areas in 13 kidneys (four right and nine left), which were mainly in the upper or lower pole (table).

Duplex kidneys—among the five patients (two boys) with seven duplex kidneys, the duplex was only recognised on the DMSA scan in two. In one girl a unilateral. scarred duplex kidney contributed 54% of the total function.

(2) Function

The differential renal function assessed on the DMSA scan correponded closely with the findings in the DTPA renogram. The figure shows the difference in the proportion of total function contributed by each kidney, expressed as a percentage in patients with unilateral and bilateral scarring. There was little disparity in individual renal function in 14 patients, even though 10 of these had unilateral scarring where a greater difference might have been expected. Eighteen patients had one small shrunken kidney and in 13 of them there was considerable disparity in function between the kidneys even in four patients in whom scarring was bilateral.

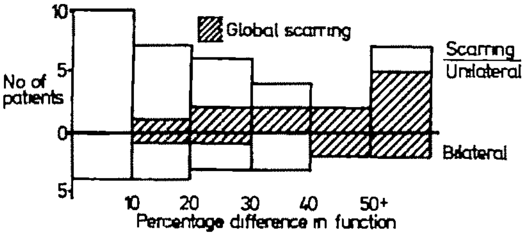

Figure *Percentage difference in function on isotope renography between right and left kidneys in 54 patients with 72 radiologically scarred kidneys Scarring was bilateral in 18 patients. No patients had bilateral global scarring*

(3) Age

Renal scarring was first diagnosed on intravenous urography in six of the children under the age of 2 years, in 24 aged 3–6 years, and in 34 aged 7–12 years. Renal scarring was well defined in the initial intravenous urogram of all of them. The first DMSA scan was carried out in two children under the age of 5 years, in nine children between the ages of 6–10 years, and in 13 children between the ages of 11–15 years. The remaining 28 were performed in patients aged 16 or over, mean age 21 years. As the DMSA scan became part of our investigative procedure, most of those performed in young children followed an acute urinary tract infection, and if the interval after this was less than three months, they were excluded from the study. There were thus not sufficient young children in the group to make a satisfactory comparison between age groups.

(4) Vesicoureteric reflux

At the time of the DMSA scan, reflux was assumed to be occurring in 27 scarred kidneys. We found no indication that vesicoureteric reflux, in the absence of infection, affected the appearance of the DMSA scan or the distribution of function.

REVIEW OF REPORTS

There was overall agreement between the intravenous urography and DMSA scan reports in 38 patients (70%) and 54 kidneys (75%) but some disagreement in the remainder. The reports of the DMSA scan would have passed seven patients with radiological scarring as normal.

Discussion

In this population of patients with established radiological scarring, the corresponding kidney was abnormal on the DMSA scan in 92%. Although discrepancies occurred in six patients, three with unilateral and three with bilateral scarring, the scarring would have been missed only in two patients if the intravenous urography had been omitted.

In six kidneys with mainly polar scars the DMSA scan was considered to be normal, but apart from the site of the scarring there were no differences of age, sex, laterality, or presence of vesicoureteric reflux to distinguish them from the other kidneys studied. When the extent, site, and severity of the scarring was considered in the whole group there was very close agreement in 63% of kidneys, but the number of scars was underestimated by the DMSA scan appearances in 30%. No additional scars unsuspected on intravenous urography were detected, even on oblique views by the DMSA scan. Contrary to the observations of Monsour *et al*, who found the left kidney to be scarred more often than the right,[5] our series included 42 right and 30 left scarred kidneys. On reviewing 119 children with 162 scarred kidneys seen in our department there were 86 right and 76 left kidneys affected. The preponderance of right kidneys in our series is not significant. Interestingly, the three radiologically unscarred kidneys with 'suspicious' DMSA scans were all left kidneys, two due to splenic impressions and one with slight patchy reduction in isotope uptake.

There were few young children in our study population because patients investigated within three months of a urinary tract infection were excluded from the study. The patchy and sometimes extensive impairment of DMSA or ^{99m}Tc glucoheptonate uptake seen after an acute urinary tract infection in a child may be of great importance in identifying those at risk of progressive renal damage and therefore in need of careful supervision, further investigation, and continued antibacterial prophylaxis until the underlying cause has been clarified [4 6 8–11] These changes may be transient and probably represent the acute inflammatory stage, which may either resolve or progress to permanent renal scarring. With adequate, rapid treatment the progress may be arrested as in the piglet and r models.[12 13] In these it was shown that by introdu ing antibacterial treatment soon after infection the refluxing urinary tract the renal scarring proce could be stopped or even prevented. (This is or explanation of the areas of slight parenchym thinning overlying slightly flattened calyces occ sionally seen on intravenous urography in childre with vesicoureteric reflux and which do not progre to classical scars.) It is thus of some importance t recognise these potentially reversible inflammato changes on the DMSA scan and differentiate the from permanent changes due to scarring. Scars ma take several months to develop: the exact time is n known clinically, and radiological observations hav depended upon the time interval between seri intravenous urograms. Scars will not be immediatel apparent on intravenous urography, althoug evidence of acute inflammation can be recognise by renal enlargement and a locally impaire nephrogram.[14 15] The presence and severity vesicoureteric reflux appeared to have no effect o the DMSA scan findings in the absence of rece infection.

Differences in function between the two kidne were related to the extent of scarring in each kidne In 10 of the 36 patients with unilateral scarring th difference in function between the two kidneys w less than 10%, indicating that such a small diffe ence does not exclude the presence of scarrin Further, there may be confusion when a unilater scar involves a duplex kidney as this may sti contribute a higher proportion of the total functio than the normal kidney. As expected, those wit severe unilateral scarring had greater relative diffe ences in renal function, but even when scarring w bilateral there could be a disparity of 40–50% if on kidney was severely scarred. The differential fun tion could thus be helpful in patients with seve scarring and in some with unilateral scarrin Urinary infection can, however, cause a pronounce depression of renal function in a scarred kidney wi persistent reflux and where this is unilateral, a difference in function will be accentuated. The observations emphasise the importance of relatin functional findings on isotope renography to th clinical history and timing of infection, and pursuing further investigations if the DMSA scan abnormal.

The DMSA scan is useful in detecting ren abnormalities in infants and young children when technically satisfactory intravenous urogram may difficult to achieve. It will indicate the relati function of the kidneys and there will be le exposure to radiation than from a full intraveno urogram with a large series of films. It is, howeve an expensive and lengthy procedure, often needing day admission, and gives little information about possible contributory causes of urinary tract infection or renal scarring.

On the other hand the intravenous urogram has the advantage to the clinician of providing a morphological renal image that is reproducible for growth assessment. It can also indicate possible factors concerned in the pathogenesis of urinary tract infection and the scarring process, including bowel and bladder function as well as any spinal anomalies. It is a less expensive investigation, still universally available and comparable, and completed in a brief outpatient visit. Radiation exposure can be minimised by careful preparation and by restricting the number of films and focusing on the renal area. The use of non-ionic contrast medium reduces the risk of side effects.

In conclusion we have found the intravenous urogram and the DMSA scan to be complementary investigations in the assessment of patients with renal scarring. The former provides structural and the latter functional information. It is important, however, for the clinician to review both sets of images together, as well as receiving reports of the differential function; any history of recent infection must be taken into account in their interpretation.

We are grateful to the National Kidney Research Fund and the Children Nationwide Medical Research Fund for their financial support; to Professor PJ Ell, Mrs Jackie Langford, and Miss Sue Huggett for the nuclear imaging, and to Mrs Jan Port and Mrs Joan Baker for secretarial help.

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Accepted 31 May 1988

Archives of Disease in Childhood, 1988, **63,** 1320–1325

^{99m}Tc dimercaptosuccinic acid (DMSA) scan as first investigation of urinary tract infection

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SUMMARY A total of 115 children under 5 years who presented with a first symptomatic urinary tract infection and who had a ^{99m}Tc dimercaptosuccinic acid (DMSA) scan were studied to assess its value and compare the findings with those of other imaging techniques. Renal cortical defects were detected in 65 kidneys by DMSA scan, intravenous urogram, and ultrasound scan combined; 62 (95%) being seen on DMSA scan. The finding of reflux on micturating cystourethrography showed a highly significant correlation with renal defects seen on DMSA scanning, a less close but still significant correlation with abnormalities on intravenous urography, but none with ultrasound scan findings. The sensitivity of the DMSA scan in screening for all grades of reflux is estimated as 0·66, which is higher than that previously reported for the intravenous urogram or ultrasound scan. DMSA scans were less likely to miss grade 3 reflux than the other two methods.

DMSA scans are more useful than other upper renal tract imaging techniques in detecting renal defects. Consideration should be given to their use as a first investigation in place of routine intravenous urograms. Ultrasound scans alone will overlook potentially serious urinary tract abnormalities.

Despite the acknowledged importance of investigating symptomatic urinary tract infection in children[1] there is still considerable disagreement as to which investigations should be undertaken after the first infection in different age groups of children. The aims of investigation should be to detect the presence of renal damage and the presence of those conditions that may predispose to renal damage, that is, vesicoureteric reflux, obstruction, and renal stones. Recent papers have compared the use of ultrasonography with intravenous urography[2] or have considered the ^{99m}Tc dimercaptosuccinic acid (DMSA) scan as only a second line investigation.[3] It has now been suggested, however, that DMSA scans should be used in the 1–7 year age group together with ultrasound scans.[4]

It is believed that most renal scars are established by 5 years of age.[5] From 1982 onwards we have been using the DMSA scan as a first line investigation in children presenting with their first symptomatic urinary tract infection under this age; this paper reports our initial experience of the scans alongside other imaging techniques.

Patients and methods

Over a three year period (1982–4) 115 children under the age of 5 years presented with symptomatic urinary tract infection that had been proved with a urinary culture of greater than 10^5 organisms/ml of urine in the presence of pyuria on one occasion or in the absence of pyuria on two occasions as suggested by Kass.[6] A group of paediatricians were invited to refer children for a DMSA scan as part of an investigation protocol in which the upper renal tract was investigated before considering a micturating cystourethrogram. The criteria for performing these investigations were not rigidly defined. In general micturating cystourethrography was performed if upper tract imaging was abnormal, although some paediatricians performed them in all children below 1 year of age. Intravenous urograms or ultrasound scans, or both, were performed according to the paediatricians' preference. All 115 children had DMSA scans, 92 had intravenous urograms, 57 had ultrasound scans, and 65 had micturating cystourethrograms.

The characteristics of the study population are shown in table 1 where they are divided into two groups depending on whether or not they had a micturating cystourethrogram. There was no significant difference between the two groups in terms of mean age, age grouping, or sex ratio.

Intravenous urograms were performed after a laxative the previous evening and restricted fluid for five to eight hours before the examination depending on age. They consisted of a full length control film, films of the renal area at 5 and 10 minutes after injection of 20–40 ml Hypaque or Niopam, and full length films before and after micturition. Renal scarring and renal size were recognised by the criteria of Hodson[7]; significant dilatation of the collecting system or the ureter on the post-micturition film and other features associated with reflux, such as striation of the renal pelvis, were recorded.

Ultrasound scans of the kidneys were performed in anterior and posterior sagittal and transverse planes using a 5 mHz transducer and a static B scanner (Philips) or latterly a real time scanner (Advanced Diagnostic Research) in which coronal planes were also obtained. Transverse scans of a full bladder were employed to visualise dilatation of the ureters. Renal length was measured and any focal cortical abnormality recorded. Separation of the renal sinus echoes by more than 0·5 cm was recorded as a dilated upper tract.

Table 1 *Age, age group, and sex of children in study*

	No micturating cystourethrogram	*Micturating cystourethrogram*
No of children	50	65
Male/female	14/36	21/44
Age		
0–11 months	22	24
12–35 months	18	24
36–59 months	10	17
Mean age (years) (95% confidence intervals)	1 68 (1 30 to 2·05)	1·70 (1·36 to 2 04)

DMSA scans were performed two to three hours after the intravenous injection of 2 MBq/kg ^{99m}Tc DMSA (minimum dose 20 MBq; maximum dose 160 MBq) (Compagne Oris Industry). Images were acquired in the posterior and both posterior oblique projections, with the child lying supine directly on the collimator of a large field of view gamma camera (International General Electric) for 500 000 counts or five minutes per view. Analogue images were used for reporting, although enhanced digital images could highlight focal abnormalities of the cortex. Defects were reported if there was a clear interruption in the renal outline on the posterior or oblique projections. Care was taken in the interpretation of movement artefacts at the renal poles and the variation in medullary uptake was ignored. Any appreciable discrepancy in renal size was noted

Table 2 *No of abnormalities detected on imaging in 115 children (230 kidneys)*

DMSA scan		*Intravenous urography*		*Ultrasound scan*		*Micturating cystourethrography*	
Micturating cystourethrography performed (65 children, 130 kidneys)							
Cortical defects	55	Cortical defects	6	Cortical defects	5	Grade 1 reflux	8
Patchy uptake	5	Dilated upper tract	33	Dilated upper tract	12	Grade 2 reflux	31
Contracted kidney	6	Contracted kidney	2	Contracted kidney	2	Grade 2 reflux	21
Enlarged kidney	2	Enlarged kidney	7	Enlarged kidney	4		
		Duplex upper tract	3	Duplex upper tract	2		
		Wide ureter post-micturition	7				
Total:							
Abnormal*	66		39		17		60
Normal	64		69		45		70
Not done	0		22		68		0
Micturating cystourethrography not performed (50 children, 100 kidneys)							
Cortical defects	7	Cortical defects	1	Cortical defects	2		
Patchy uptake	1	Dilated upper tract	7	Dilated upper tract	9		
Contracted kidney	0	Contracted kidney	1	Contracted kidney	1		
Enlarged kidney	1	Enlarged kidney	3	Enlarged kidney	1		
		Duplex upper tract	3	Duplex upper tract	0		
		Wide ureter post-micturition	1				
		Stone	1				
Total:							
Abnormal*	9		12		13		
Normal	91		64		39		
Not done	0		24		48		100

*Some kidneys had more than one abnormality.

as well as relative renal uptake outside the range of 45–55% calculated by region of interest analysis after background subtraction.

Micturating cystourethrograms were performed after bladder catheterisation with a 4·5–6 FG feeding tube. Hypaque was run into the bladder slowly by gravity from a height of 100 cm. The bladder was screened intermittently during filling and the catheter removed before continuous screening during micturition. Reflux was recorded on a scale of 1 to 3 (grade 1 confined to the ureter, grade 2 reaching the renal calyces without distension, and grade 3 with distension; after Bailey[8]).

Results

Table 2 shows the abnormalities of kidneys that were detected by the four different types of investigation in the 115 children. Because micturating cystourethrograms were only performed in 65 children these results are shown separately to allow comparison of the results of upper renal tract imaging with the 50 children who did not proceed to micturating cystourethrography.

Table 3 compares the detection of cortical defects by DMSA scans and intravenous urograms in the 92 children who had both investigations. This shows that DMSA scans are significantly more sensitive at detecting defects than intravenous urograms ($p<0{\cdot}05$ by McNemar's test).

Table 4 considers only those children who had micturating cystourethrograms. The results of DMSA scans, intravenous urograms, and ultrasound scans in kidneys with reflux are compared with those without reflux. There was a highly significant correlation between the presence of cortical defects on the DMSA scan and detection of reflux on the micturating cystourethrogram ($p<0{\cdot}001$ by χ^2 with Yates's correction). There was a less pronounced but still significant correlation beteen reflux and parenchymal defects or upper tract dilation on the intravenous urograms ($p<0{\cdot}05$) but no significant correlation with the ultrasound scan findings.

Table 5 shows the results of upper tract investigations in the 21 kidneys which showed grade 3 reflux on micturating cystourethrograms. The superior correlation between grade 3 reflux and the DMSA scan ($p<0{\cdot}001$, χ^2) compared with grade 3 reflux and the intravenous urogram or ultrasound scan ($p>0{\cdot}05$) is clearly seen in this group of patients.

Discussion

DETECTION OF SCARRING

We believe that a DMSA scan is at present the most sensitive method to detect renal defects. The find-

Table 3 *Detection of renal defects in DMSA scans compared with intravenous urograms*

	With DMSA scan	*Without DMSA scan*	*Totals*
With intravenous urography	32	2	34
Without intravenous urography	23	35	58
Totals	55	37	92

$p<0{\cdot}05$ by McNemar's test

Table 5 *Screening investigations in 21 kidneys with grade 3 reflux*

	Normal	*Abnormal*	*Not done*
DMSA scan	3	18	0
Intravenous urography	9	7	5
Ultrasound scan	10	6	5

Table 4 *Comparison of screening investigations with results of micturating cystourethrography. Results are number of kidneys*

Micturating cystourethrography	*DMSA scan*		*Intravenous urography*		*Ultrasound scan*	
No reflux (n=70)	Normal	44	Normal	44	Normal	25
	Abnormal	26	Abnormal	16	Abnormal	9
			ND	10	ND	36
Reflux (n=60)	Normal	20	Normal	25	Normal	20
	Abnormal	40	Abnormal	23	Abnormal	8
			ND	12	ND	32

ND=not done.

ings on DMSA scans have been shown to correlate closely with findings on intravenous urograms,[9] though we detected far more cortical defects on DMSA scanning than by intravenous urography (table 3). A recent publication by Monsour *et al* of a series of children with proved reflux has further confirmed the accuracy of DMSA scans in detecting early renal scarring in the under 5 year age group.[10] Serial observations of intravenous urograms have suggested that it can take up to two years for scars to become evident by this method.[11 12] In our series 95% (62/65) of defects that we saw by any method were seen on DMSA scans. Of the remaining three cortical defects one was detected by ultrasonography and two, as shown in table 3, by intravenous urography. These other investigations were not performed in all kidneys with normal DMSA scans and we cannot be certain how many more cortical defects might otherwise have been detected by these means. The most favourable estimate of the results of performing urograms on all our patients, however, suggests that we would have detected nine cortical defects in the 168 kidneys reported as normal on DMSA scan at the cost of missing 26 of the 62 defects that were detected by DMSA scan.

Our total figure of cortical defects in 28% of the kidneys investigated is similar to other reported series (24–35%),[9 13] although their study populations included children over 5 years. It is likely that these cortical defects indicate renal involvement in the infective process and kidneys at risk of scarring are therefore identified soon after the infection. It has yet to be shown that all these defects will go on to develop into renal scars but Merrick *et al* have shown that in a group of children with established pyelonephritis the DMSA scan was more sensitive than the intravenous urogram in the detection of scarring.[13] It has been reported that ultrasound scans are poor at detecting small cortical defects[14] and our experience supports this view.

DETECTION OF REFLUX

As it is well recognised that there is a strong association between the presence of reflux and parenchymal scarring,[15 16] we expected that there would be a strong correlation between cortical defects on DMSA scans and reflux on micturating cystourethrograms and this is indeed the case (table 4). Previous authors have proposed that the intravenous urogram or ultrasound scan should be used to screen for significant reflux.[14 17 18] We have found the DMSA scan to be a better predictor of the presence of reflux than either of these methods.

The favourable results we obtained with the DMSA scan are open to criticism on the grounds that we are using an unrepresentative sample. Although we have shown (table 1) that there was no difference in mean age, age distribution, and sex between those children who had an micturating cystourethrogram and those who did not, the criteria used in selecting those children who proceeded to micturating cystourethrography resulted in an overrepresentation of kidneys with defects in this group. To reduce this bias we have looked at those patients who had only unilateral reflux and compared the results of the screening tests in each kidney. There were 17 such patients all of whom had a DMSA scan, 15 an intravenous urogram, and eight an ultrasound scan. There was a highly significant correlation between the finding of defects on the DMSA scan and reflux on the micturating cystourethrogram (14 of 17 in refluxing kidneys compared with three of 17 in non-refluxing kidneys; $p=0\cdot00028$, by Fishers's exact test, two tailed). The correlation for dilatation or scarring, or both, on intravenous urogram (eight of 15 with reflux compared with three of 15 without) and ultrasound scan (five of eight compared with two of eight) did not reach significance.

We then considered the patients who had unilateral cortical defects on the DMSA scan and went on to have a micturating cystourethrogram as these patients act as their own controls. In 37 patients with unilateral defects on the DMSA scan, 22 had reflux on the affected side and 11 on the non-affected side. If it is assumed that the micturating cystourethrogram does not give false negative results and that this group of patients are representative of the whole group this gives a sensitivity of 0·66, a specificity of 0·63, an accuracy of 0·65, and a significant correlation ($p<0\cdot025$, χ^2). Reported series quote intravenous urograms and ultrasound scan findings in both refluxing and non-refluxing kidneys that show a sensitivity of 0·54 and a specificity of 0·86 for the intravenous urogram in the largest series,[15] and other series show sensitivities of less than 0·5.[17 18] These last two series, however, show a sensitivity approaching 1·0 for the detection of grade three reflux; this is not borne out by our findings (table 5) or in other series.[19–21] In only seven of 16 kidneys with grade 3 reflux were there clues on intravenous urography that reflux might be present.

Our figures suggest that the DMSA scan is more sensitive than either intravenous urogram or ultrasound scan at predicting the presence of reflux. Although the intravenous urogram may be more selective, its lower sensitivity makes it less suitable as a screening test. It has been suggested that ultrasonography is not able to exclude the presence of appreciable reflux and this is confirmed by our experience in this series.[14 22] With newer equipment and greater experience the sensitivity of ultrasonography may be improved in the future. It remains true that the only way of ensuring that reflux is never missed is to perform a micturating cystourethrogram on every child and this approach has been recommended.[20] but we wonder whether this remains appropriate in view of the recent evidence that scarring rather than reflux *per se* is a more important factor in determining long term renal outlook.[23 24]

Only two children out of 14 under 1 year of age with reflux had no evidence of renal cortical defects on the DMSA scan. This confirms that young infants are particularly vulnerable to renal involvement if reflux and infection are present and we would recommend micturating cystourethrogram on all children under 1 year with a confirmed urinary tract infection.

Twenty six kidneys in 23 children showed cortical defects in the absence of reflux and these deserve further consideration as reflux should be present in over 90% of scarred kidney units.[18] We found reflux in only 57% of kidneys with defects seen on the DMSA scan. These scans were performed soon after the presentation of urinary tract infection and it has been reported that acute pyelonephritis can cause temporary abnormalities on DMSA scan for up to three months.[9] Follow up scans in 18 of these 26 kidneys, however, have now been performed at least six months after the original scan and in only six kidneys have the defects disappeared. We believe therefore that previous estimates of the occurrence of scarring in non-refluxing kidneys are an underestimate as they have relied on intravenous urography alone for the detection of scarring. Even if early scans identify one in three children whose defects are only temporary this would not weaken the argument for the DMSA scan as a screening test to detect those children who require a micturating cystourethrogram. The percentage of children who would have had a negative micturating cystourethrogram was only 43% which compares with 63% in a series using no preselection.[20] Those 12 kidneys with persistent defects suggest that scarring does occur in the absence of reflux more often than previously reported and these cases were only detected by a DMSA scan performed soon after the presenting infection.[25]

DETECTION OF OBSTRUCTION AND RENAL STONES

Ten cases of unilateral dilatation of the urinary tract were detected by intravenous urography. The DMSA scan was abnormal in all 10 cases, showing cortical defects in five, enlarged kidneys in three, and appreciably reduced split function in two. Seven of these cases also had an ultrasound scan of which five showed pronounced dilatation, one showed cortical scarring, and one was reported to be normal.

One patient in our series had a renal stone detected on the control film of the intravenous urogram. In this case the DMSA scan showed a cortical defect, although we would not expect the DMSA scan to be a reliable method of detecting stones.

CONCLUSIONS

We believe that given the available equipment and expertise DMSA scans are a most useful first investigation of urinary tract infection. In view of the non-invasive nature of ultrasonography and the increasing experience in its use we would recommend its retention also as a first line investigation as it is a reliable method of detecting structural abnormalities of the urinary tract. In our view, however, the use of ultrasound alone in the under 5 age group will overlook potentially serious urinary tract abnormality. We would suggest that those children who have abnormal DMSA scans proceed to micturating cystourethrography as two thirds of them will have reflux. If this approach is adopted the role of the intravenous urogram as a primary modality of investigation becomes questionable. Undoubtedly the occasional child with reflux will be missed but this would be true whatever combination of screening tests was used. Further prospective studies are needed to establish whether reflux in the absence of scarring is ever of any long term importance but we are reluctant to subject all children with urinary tract infection to micturating cystourethrography in our present state of knowledge. As well as being an unpleasant procedure it exposes the gonads to about 10 times the irradiation of a DMSA scan.[26] The unique ability of the DMSA scan in detecting the presence of kidney defects makes it a valuable research tool in defining those children who sustain renal damage with urinary tract infection and thus helps clarify the factors that put them at risk; newly developed methods for image presentation may further enhance sensitivity.[27] More widespread use of this technique should lead to a better understanding of the natural history of renal scars and allow earlier detection of children at risk of progressive renal damage.

We thank the consultant paediatricians of Merton and Sutton, Mid-Surrey, and East-Surrey health authorities for referring their patients for investigation and Dr VR McCready and the staff of the department of nuclear medicine, Royal Marsden Hospital, for performing the scans

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Accepted 29 May 1988

Archives of Disease in Childhood, 1988, **63,** 1326–1332

Growth and endocrine function after renal transplantation

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SUMMARY Longitudinal height data and physical development were assessed in 45 boys and 34 girls after renal transplantation. All children received alternate day steroids and either azathioprine or cyclosporin A for immunosuppression. There was a significant increase in growth velocity after transplantation in prepubertal children. Growth velocity declined at the expected age of the normal pubertal growth spurt, however, with delay in the appearance of secondary sexual characteristics. Overnight hormone profiles in 17 adolescent subjects with short stature or maturational delay, or both, showed blunting of growth hormone and gonadotrophin pulsatility. It is likely that long term steroid treatment after renal transplantation induces the clinical and endocrine picture of delayed puberty. Failure of growth to accelerate at this time is a cause of short stature, which may have an effect on adult height.

Growth failure is an important consequence of chronic renal failure for many children. Mean adult height is reduced on average by two standard deviations for those transplanted before the age of 15 years. Delayed puberty is also a common finding; half the girls and one third of boys reach sexual maturity later than 95% of the normal population [1] After renal transplantation many children have an appreciable improvement in their growth. Our impression, however, was that the initial increased growth rate was not sustained during the ensuing years of immunosuppressive treatment

In boys taking long term steroid treatment for steroid sensitive nephrotic syndrome, we observed a clinical picture of delayed puberty, with blunting of the secretion of growth hormone and gonadotrophins Immunosuppression with steroid treatment may, therefore, cause a decline in growth velocity at the time of the expected pubertal growth spurt,[2] and account for the lack of continuing growth improvement after renal transplantation

We analysed retrospectively the growth and pubertal development of our current population of children and adolescents with renal transplants. We also investigated the endocrine function of 17 of the adolescents who had growth retardation or pubertal delay, or both

Patients and methods

All children attending Guy's Hospital paediatric renal transplant clinic at the end of May 1987, and who had had a functioning graft for at least a year, were included in the study (45 boys, 34 girls). The causes of chronic renal failure were: obstructive uropathy (n=18, 24%), dysplasia (n=13, 16%), focal segmental glomerulosclerosis (n=9, 11%), proliferative glomerulonephritis (n=9, 11%), nephronophthisis (n=8, 10%), reflux nephropathy (n=7, 9%), cystinosis (n=5, 6%), and miscellaneous (n=10, 13%).

The immunosuppressive treatment used was broadly divided into two groups: high dose prednisolone (30 mg/m^2 on alternate days) and azathioprine (regimen 1) or low dose prednisolone (10 mg/m^2 on alternate days) and cyclosporin A (regimen 2). There was overlap in steroid dose between the two groups, however: many patients on regimen 1 with live related transplants and stable graft function had their steroid dose reduced, and patients on regimen 2 with poorly functioning grafts had their steroid treatment increased. Furthermore, over the years several children switched regimen. Rejection episodes were managed in the same way for each regimen: methyl prednisolone 600 mg/m^2 for three consecutive days during the first six weeks post transplant, and oral prednisolone 3 mg/kg/day for three days after the first six weeks.

The following were obtained from the notes and on examination:

(1) Chronological age at transplantation (years).

(2) Height (cm) at the time of transplantation and subsequently at yearly intervals For each subject the height standard deviation score (Ht SDS) was calculated, according to the formula Ht SDS=$(x-\bar{x})$/SD, where $\bar{x}$ and SD are age matched population mean height and SD respectively and x is the subject's height. The height velocity standard deviation score was calculated for each post transplant year in each subject. Normal population data were according to Tanner *et al.*[3]

(3) Bone age (TW2) and puberty rating[4] in children over the age of the third centile for appearance of secondary sexual characteristics (boys >14·0 years, girls >13·3 years).

Eleven children were transplanted before the age of 10 years and were over the age of 14 years. Their calculated glomerular filtration rate (ml/min/1·73^2)[5] was compared at 11 and 14 years of age.

An overnight hormone profile study was performed in 13 boys and four girls who were short (<10 centile), and/or growing poorly (height velocity <25 centile) and/or delayed in puberty (<10 centile for age). The steroid dose (mg/m^2) and the glomerular filtration rate at the time of the study was calculated.[5] Height velocity (cm/year) and height velocity SDS were calculated for the six months before the study (table 1). Studies were performed on the day off steroids in all patients except 13, 14, 15 and 17. Subjects 1 and 6 were taking daily steroids. Each study commenced at 18·00 hours, when an indwelling cannula was inserted into a forearm vein. Adequacy of sleep was analysed using a portable continuous electroencephalograph (Oxford Medilog System).[6] Blood samples were taken every 20 minutes from 20·00 hours through to 07·00 hours (3 ml blood per sample). Plasma was subsequently stored at −20°C until assay. Growth hormone (mU/l), gonadotrophins (luteinising hormone, follicle stimulating hormone, IU/l), and prolactin were measured on each sample and testosterone (nmol/l) and insulin like growth factor 1 (U/ml) on intermittent samples through the night. All samples from each profile were batch analysed. Growth hormone was measured by radioimmunoassay using the first International Reference Preparation 66/217, with an intra-assay coefficient of variation of 5·0% and 2·4% at 10·8 and 20·4 mU/l respectively and an interassay coefficient of variation of 10% at 7·5 mU/l. Gonadotrophins were measured by radioimmunoassay using the first International Reference Preparation of luteinising hormone 68/40 and follicle stimulating hormone 78/549, with an intra-assay coefficient of

Table 1 *Patient details at the time of the overnight hormone profiles*

Patient No	*Alternate day steroid dose (mg/m^2)*	*Cyclosporin A*	*Age at transplant (years)*	*Chronological age (years)*	*Bone age (years)*	*Genital stage*[4]	*Height SDS*	*Height velocity SDS*	*Height velocity (cm/year)*	*Glomerular filtration rate (ml/min /1·73 m^2)*
					Girls					
1	4·4*	+	13·1	13·3	9·6	1	−4·9	0·4	6·1	80
2	10·9	+	11·0	11·7	8·0	1	−3·3	−2·3	2·3	49
3	13·2	+	11·9	14·2	12·4	3	−3·5	1·2	5·9	37
4	22·2	−	14·7	18·4	13·8	5	−3·1	—	0·5	58
					Boys					
5	4·9	+	12·6	14·4	10·4	1	−4·2	−1·9	3·4	30
6	3·9*	+	14·7	15·2	14·5	3	−2·4	−0·4	5·1	20
7	8·7	−	8·8	17·5	15·3	2	−2·5	6·0	7·6	92
8	8·8	+	7·6	13·0	12·2	1	−2·3	−0·7	4·2	33
9	8·8	−	8·0	14·5	12·4	2	−2·3	−2·7	1·8	76
10	9·1	−	8·5	16·3	12·8	2	−4·2	0·6	5·0	86
11	9·2	+	12·0	13·7	12·0	1	−1·4	−1·5	3·6	64
12	13·0	−	7·6	14·8	13·5	2	−2·4	−1·2	4·6	84
13	17·1	+	11·2	13·3	11·0	1	−1·9	−1·2	3·8	24
14	17·7	−	11·3	12·9	9·5	1	−3·0	−0·7	4·6	31
15	23·6	−	15·0	16·9	14·5	2	−4·0	2·2	5·5	53
16	24·6	−	15·8	17·6	12·7	1	−6·0	2·9	1·4	50
17	26·0	−	12·9	15·5	15·7	3	−1·4	−1·9	1·4	42

*Daily steroid dose

variation of (a) luteinising hormone, 8·8% and 10% at 2·4 and 15·0 IU/l and (b) follicle stimulating hormone 10·3% and 7·3% at 2·8 and 14·9 IU/l respectively. Prolactin was measured by radioimmunoassay using the first International Reference Preparation of 75/504. Testosterone was measured by standard kit method (Diagnostic Products Corporation). Serum insulin like growth factor 1 was measured by radioimmunoassay after acid-ethanol extraction.[7] Antiserum R557A and insulin like growth factor labelled with ^{125}I[8] were kindly provided by Dr DJ Morrell (Institute of Child Health, London). Intra-assay and interassay coefficient of variation were <8% and <10% respectively. Values for insulin like growth factor 1 were expressed as potency relative to pooled normal adult human reference serum defined as 1 unit insulin like growth factor 1/ml.

Growth hormone and gonadotrophin hormone peak analysis was performed both visually and using the 'Pulsar' programme,[9] which was modified locally to include a calculation of area under the curve by summation of trapezoids

STATISTICAL ANALYSIS

By definition, the mean SDS of the normal population is zero, and the standard deviation of the distribution is one. Our data were symmetrically distributed; for purposes of statistical comparison with the normal population, the mean and standard deviation of each subgroup of patients was calculated. Comparison of height velocity SDS at various age groupings was by one way analysis of variance. Comparison of glomerular filtration rate at 11 and 14 years of age was by paired *t* test. Comparison of the association of overnight hormone profile measurements with height velocity, glomerular filtration rate, and steroid dose was by Pearson product moment coefficient. Results are expressed as mean (SE), together with range where appropriate

Results

GROWTH DATA

The mean age (range, years) at transplantation for the boys was 8·3 (0·8–15·8). They were significantly short at the time of transplantation (height SDS −2·87 (0·25), p<0·001) compared with the normal population. The mean (range) duration of follow up (years) was 3·6 (1·0–10·0). At the end of follow up they were significantly short (height SDS −2·24 (0·25), p<0·001). In the girls age at transplantation was 9·6 (1·7–14·7), with a height SDS of −2·10 (0·24), p<0·001. Duration of follow up was 3·2 years (1·0–8·0), with a height SDS at the end of follow up of −2·12 (0·27), p<0·001.

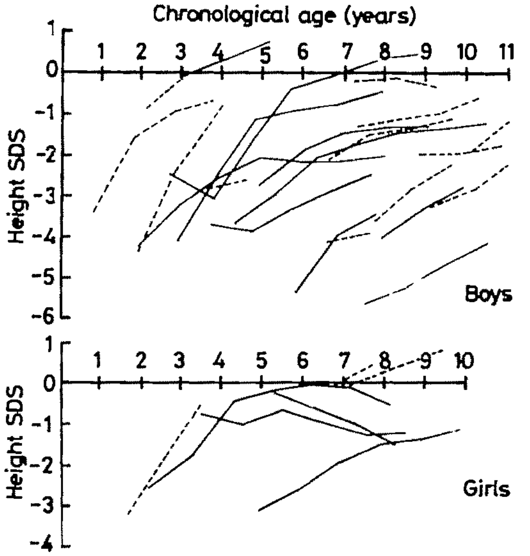

Fig 1 *Height SDS at the time of transplantation and at yearly intervals for the 21 boys aged less than 11 years and the seven girls aged less than 10 years at the end of May 1987 (- - - steroids plus cyclosporin A, ——— steroids plus azathioprine).*

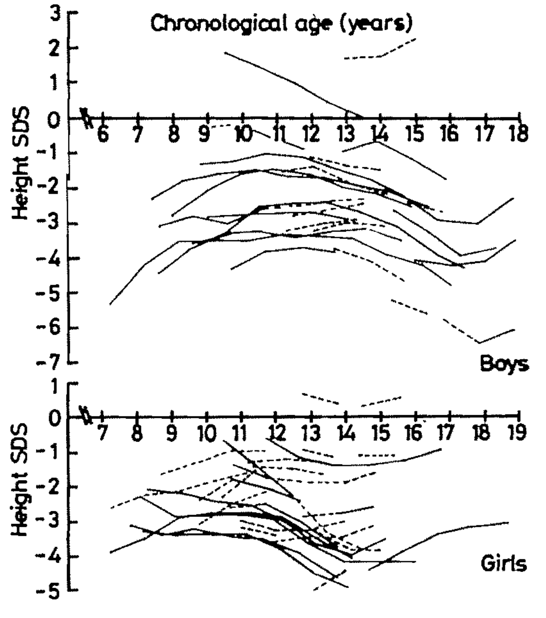

Fig 2 *Height SDS at the time of transplantation and at yearly intervals for the 24 boys aged over 11 years and the 27 girls aged over 10 years at the end of May 1987 (- - - steroids plus cyclosporin A, ——— steroids plus azathioprine).*

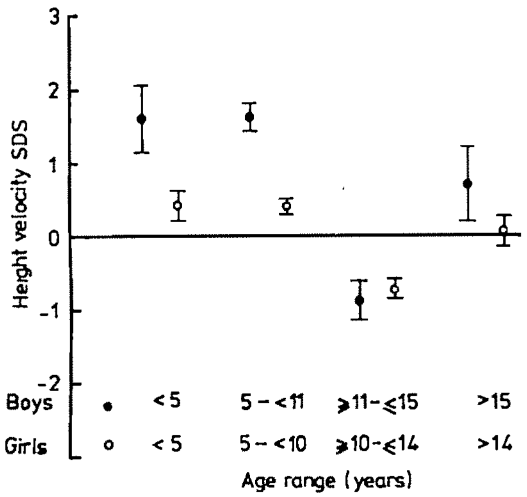

Fig 3 *Mean (SE) height velocity SDS at different age ranges post renal transplantation*

Height SDS at the time of transplantation and at yearly intervals thereafter are shown for the prepubertal children in fig 1, and for the older children in fig 2. An arbitrary division at the age of 11 years in the boys and 10 years in the girls at the time of the last examination was chosen to examine the effect of puberty. In both boys and girls after the initial improvement in height SDS there was a subsequent fall at the time of the expected pubertal growth spurt, with the beginning of a recovery in some adolescents near adulthood. There appeared to be no difference in the growth patterns between immunosuppressive regimens 1 and 2.

To examine the effect of puberty on growth more closely, both sexes were subdivided into the following chronological age groups (years): boys, <5, 5–<11, ≥11–≤15, and >15; girls, <5, 5–<10, ≥10–≤14, >14. Height velocity SDS at yearly intervals from the time of transplantation was measured in each subject and the mean for all subjects calculated in each age grouping. The results are shown in fig 3. In the boys height velocity SDS at yearly intervals was significantly greater compared with the normal population in age group <5 (1·58 (0·46), $p<0{\cdot}001$) and 5–<11 (1·58 (0·22), $p<0{\cdot}001$); at age 11–≤15 it was significantly less (−0·88 (0·26), $p<0{\cdot}001$); after 15 there was no significant difference (0·68 (0·52)) The height velocity SDS in the ≥11–≤15 age grouping was significantly lower compared with the other age groups ($F=18{\cdot}6$, df between groups was 3 and within groups was 162, $p<0{\cdot}01$). A similar picture was seen in the girls with a high height velocity SDS compared with the normal population in age groups <5 (0·41 (0·20), $p<0{\cdot}05$) and 5–<10 (0·40 (0·10), $p<0{\cdot}001$), a decrease in age group ≥10–≤14 (−0·74 (0·12), $p<0{\cdot}001$) and no significant difference in girls >14 (0·04 (0·23)). The height velocity SDS in the ≥10–≤14 age group was significantly lower compared with the other age groups ($F=8{\cdot}82$, df between groups was 3 and within groups was 105, $p<0{\cdot}01$). There was no significant difference between the glomerular filtration rate (ml/min/1·73 m^2) at age 11 years (60 (3·6)) and at age 14 years (65 (5·5)), and no correlation between height velocity and glomerular filtration rate in the children undergoing overnight profiles.

Ten of the 16 boys over the age of 14·0 years and six of the 19 girls over the age of 13·3 years were below the third centile for pubertal development.[4] Bone age compared with chronological age (both in years) in these subjects was delayed in both sexes; mean bone age minus mean chronological age (range): boys −2·0 (−4·0 to 0·0), girls −1·1 (−4·8 to 1·2).

OVERNIGHT HORMONE PROFILES

Clinical details of the subjects in whom overnight profiles were performed are given in table 1. All subjects slept through the study with normal patterns on electroencephalography.[6] Data of hormone profiles from a control group were lacking. Various studies over the last 15 years, however, have suggested an appreciable increase in pulsatility of growth hormone and gonadotrophins during the age range associated with normal puberty.[10–15] Visual comparison with these documented profiles and profile analysis suggested that one girl (patient 4) and seven boys (patients 5, 9, 11, 12, 13, 16, and 17) had decreased secretion of growth hormone (table 2). There was a significant correlation between the height velocity over the previous six months (cm/year) and area of growth hormone under the curve (mU/l/hour) ($r=0{\cdot}60$, $p=0{\cdot}01$), the mean growth hormone concentration ($r=0{\cdot}60$, $p=0{\cdot}01$), and the growth hormone mean peak amplitude ($r=0{\cdot}80$, $p=0{\cdot}0001$). There was no correlation between either the steroid dose (mg/m^2) or the glomerular filtration rate and growth velocity or any parameters of growth hormone All concentrations of insulin like growth factor 1 were within normal limits for age and sex. Secretion of luteinising hormone was low in two girls (patients 1 and 2) and six boys (patients 9, 12, 13, 15, 16, and 17), with reduced pulsatility in one other boy (10). There was no correlation between the area of luteinising hormone under the curve (IU/l/hour), mean luteinising hormone concentration or mean peak amplitude of luteinising hormone and either height velocity, glomerular filtration rate, steroid dose, or any parameters of growth hormone. Follicle stimulating

Table 2 *Overnight hormone profile analysis for growth hormone and insulin like growth factor 1 concentrations in 17 adolescents with renal transplants*

Patient No	*Area under curve (mU/l/hour)*	*Mean growth hormone (mU/l)*	*Pulses*		*Mean insulin like growth factor 1 (U/ml)*
			No	*Mean amplitude (mU/l)*	
			Girls		
1	1154	18 9	5	43·2	1 7
2	697	11 4	5	16·6	2 1
3	1130	18·3	3	30·5	1 8
4	90	1 6	3	2·2	1 9
			Boys		
5	226	3·8	3	8 6	1 1
6	2606	41·9	3	50 0	1 5
7	1329	20·2	3	47 7	1·6
8	1156	19 0	4	30·5	1 9
9	351	5 4	5	12·9	2·2
10	469	7·8	3	17·7	1 8
11	102	1·7	3	2 3	1 1
12	185	3 4	3	10 6	1 4
13	212	3 5	2	9 0	1·3
14	862	14 1	2	27 8	1 9
15	999	17·2	4	33 7	3 4
16	107	1 8	1	8·6	1 3
17	331	5 5	1	16 7	2 0

hormone concentrations was low, with reduced pulsatility in one girl (patient 2) and nine boys (patients 5, 7, 8, 9, 10, 12, 13, 14, and 16). Concentrations of testosterone were below 3·0 nmol/l in eight boys. Testosterone correlated significantly with the area of growth hormone under the curve (r=0·83, p=0·0004), mean growth hormone concentration (r=0·83, p=0·0005), and mean peak amplitude of growth hormone (r=0·75, p=0·002). Testosterone was only weakly correlated with the area of luteinising hormone under the curve (r=0·50 p=0·08), mean luteinising hormone concentration (r=0·50, p=0·08), and mean peak amplitude of luteinising hormone (r=0·60, p=0·035) but not with luteinising hormone pulse number. There was no correlation between testosterone and height velocity or glomerular filtration rate. Prolactin secretion was within normal limits for all subjects (table 3). Examples of the overnight profiles from two boys of similar age and both in mid puberty are shown in fig 4 Patient 6 was growing at a rate of 5·1 cm/year and had normal growth hormone and luteinising hormone pulsatility, whereas patient 17, who was growing at only 1·4 cm/year had pronounced blunting of growth hormone and gonadotrophin secretion.

Discussion

We have shown that acceleration of growth can be

Table 3 *Overnight profile analysis for luteinising hormone, follicle stimulating hormone, testosterone, and prolactin Results are mean (range)*

Luteinising hormone				*Follicle stimulating hormone*				*Testosterone (nmol/l)*	*Prolactin (mU/l)*
Area under curve (IU/l/hour)	*Mean (IU/l)*	*Pulses*		*Area under curve (IU/l/hour)*	*Mean (IU/l)*	*Pulses*			
		No	*Mean amplitude*			*No*	*Mean amplitude*		
					Girls				
397 (83–1057)	6 7 (1 4–17·7)	2 (0–4)	2 7 (0–6 4)	277 (77–475)	4 6 (1 3–7 8)	6 (0–10)	1·9 (0–4 5)	—	397 (103–809)
					Boys				
255 (51–460)	4·3 (1 0–7·7)	2 (0–5)	2 1 (0–5·6)	127 (54–272)	2·1 (0 9–4·7)	2 (0–11)	0·6 (0–2·7)	4·3 (0 3–21 3)	235 (111–388)

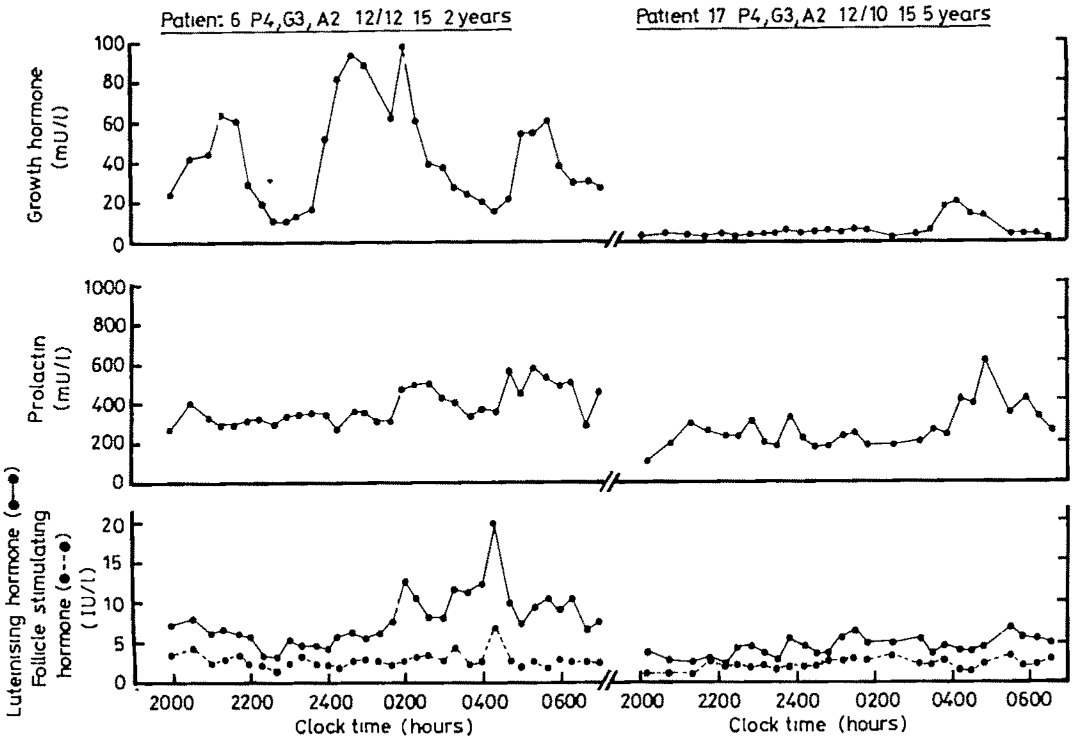

Fig 4 *Overnight hormone profiles in a boy who is growing satisfactorily (patient 6) and in a boy who is growing poorly (patient 17). P=pubic hair stage, G=genital stage, A=axillary hair stage, -/-=testicular volumes.*[4]

achieved in prepubertal children after renal transplantation, as suggested previously from our own[16] and other centres.[17] [18] Recent studies have suggested better growth rates in patients taking cyclosporin A and low dose steroids than in those receiving azathioprine and high dose steroids.[19] [20] Multiple confounding factors, however, such as heterogeneity of diagnoses, age at onset of chronic renal failure, age at transplantation, number of rejection episodes, graft function, bone age, the onset of puberty, live related or cadaver donor, and in our patients alteration of the immunosuppressive regimen over the years, makes us reluctant to investigate the question with our data. Visual inspection of the growth patterns does not, however, show any obvious difference, and there is no correlation between growth rates and steroid dose in the adolescents undergoing overnight profiles.

It is clear that after the initial acceleration prepubertally, growth velocity declines in early adolescence and there is a delay in both boys and girls in the appearance of secondary sexual characteristics. Poor growth during puberty has been reported previously.[21] Deteriorating allograft function did not contribute to this declining growth rate in our adolescents. The onset of normal puberty is associated with increasing pulsatility of both growth hormone and gonadotrophin secretion.[10–15] Appreciable blunting of both growth hormone and gonadotrophin secretion was seen in a high proportion of our subjects, who were studied because of short stature or delayed puberty or both. Concentrations of insulin like growth factor 1 were normal, but their interpretation in renal disease is unclear.[22] Concentrations of plasma testosterone were low in over half the boys studied. There was no evidence that prolactin (which at high levels has been reported to decrease luteinising hormone pulsatility in men[23]) was responsible, as values were within normal limits.[24]

Abnormalities of pubertal growth and hormone secretion do not appear to be a feature of chronic renal failure itself.[22] [25–27] We have observed, however, blunting of the overnight secretion of growth hormone and gonadotrophins in boys receiving long term steroid treatment for steroid sensitive nephrotic syndrome.[2] This was also associated with the delayed onset of puberty. It is likely, therefore, that long term steroid treatment interferes with the onset and progression of puberty and the pubertal growth spurt. The results of the overnight hormone profiles indicated that the interference is central, at the hypothalamic-pituitary end of the axis. The effect this may have on the final height of children who have had renal transplants remains unknown; it is possible that the benefits of the initial good response in growth is lost to the steroid effects on the pubertal growth spurt The picture of delayed puberty, however, has severe implications in the clinical management after renal transplantation.

All the transplant patients received long term alternate day steroid treatment as part of their immunosuppressive regimen, although as discussed the dose of steroids varies considerably. Given our findings it may be advisable to attempt to reduce the steroid treatment to absolute minimum in those children approaching the expected onset of puberty. Indeed, in children with longstanding transplants and stable function, who are showing a declining growth rate, it may be advisable to use an immunosuppressive regimen that excludes steroids. Alternatively, it may be appropriate to attempt to improve growth with low dose anabolic steroid treatment or with growth hormone itself.

This work was supported by the Children's Nationwide Medical Research Fund. SAG is supported by the Wellcome Trust, PA by grants from Serono Laboratories (UK) and the Child Growth Foundation, and JJ by a grant from the Adint Trust We thank Dr Charles Buchanan for analysis of insulin like growth factor 1, Miss G Wilson and Mrs J Jenkins for the recordings of electroencephalography, and the sister and nursing staff of Peter Bishop metabolic ward.

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Accepted 6 May 1988

Archives of Disease in Childhood, 1988, **63,** 1333–1338

Motor disorders of the oesophagus in gastro-oesophageal reflux

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SUMMARY Mechanisms of gastro-oesophageal reflux were studied by oesophageal manometry and pH monitoring in 33 children: nine controls, 15 with gastro-oesophageal reflux alone, and nine with reflux oesophagitis. A total of 122 episodes of reflux were analysed in detail: 82 (67%) were synchronous with swallowing and 40 (33%) asynchronous. Infants with trivial symptoms had gastro-oesophageal reflux synchronous with swallowing, whereas those with serious symptoms had slower acid clearance and asynchronous reflux. There were significant differences in lower oesophageal sphincter pressure and amplitude of oesophageal contractions between controls and patients with both gastro-oesophageal reflux and reflux oesophagitis. In reflux oesophagitis there was a decrease in lower oesophageal sphincter pressure and the contractions had a bizarre waveform suggesting a neuropathic process.

Gastro-oesophageal reflux is a common condition in infants and children that may be associated with significant morbidity due to an impaired energy intake, repeated pulmonary aspiration, and recurrent haemorrhage secondary to oesophagitis.[1]

Previously lower oesophageal sphincter activity has been regarded as crucial in the pathophysiology of gastro-oesophageal reflux, but this is probably an oversimplification. It is likely that mechanisms of gastro-oesophageal reflux involve the interplay of oesophageal motility, lower oesophageal sphincter activity, and gastric emptying. Disturbance of the mechanisms of clearance of gastric contents refluxed into the oesophagus may thus result from perturbation of the oesophageal motor apparatus. It has been suggested that spontaneous relaxation of the lower oesophageal sphincter in the absence of a preceding oesophageal peristaltic sequence ('inappropriate relaxation') is an important mechanism in gastro-oesophageal reflux, which may represent disturbed integrity of the oesophageal motor apparatus and be more important than reduced basal lower oesophageal sphincter pressure alone.[2]

In this study, motor function of the oesophagus, acid clearance, and the effects on oesophageal motility of exposing the oesophagus to endogenous acid, were assessed to evaluate the relationship between the disorders associated with gastro-oesophageal reflux described above and the motor mechanisms responsible for gastro-oesophageal reflux in patients with and without oesophagitis.

Patients and methods

Thirty three patients (age 3 months–14 years, median 2 years) with symptoms suggestive of gastro-oesophageal reflux were investigated by barium meal, 24 hour oesophageal pH monitoring, oesophageal manometry, and endoscopy. Gastro-oesophageal reflux was diagnosed by oesophageal pH monitoring and by the presence of reflux on barium meal examination. Nine patients (age 3 months–2 years) presented with feeding problems and failure to thrive; they did not have evidence of gastro-oesophageal reflux on pH studies or on barium meal and served as controls. Fifteen patients (age 3 months–4 years) had appreciable gastro-oesophageal reflux on barium meal and pH study but did not have endoscopic evidence of oesophagitis; three of these patients had severe feeding problems and four recurrent respiratory problems. A further nine patients (age 1–14 years) were studied who had gastro-oesophageal reflux and appreciable oesophagitis on endoscopy. Four of the latter group have a major neurological condition: spastic quadriplegia or hydrocephalus.

Twenty four hour oesophageal pH studies were performed using an antimony pH electrode (Synectics Medical) that was positioned in the oesophagus at the level of T10 using fluoroscopy, it was connected to a pH meter. the output of which was digitalised and stored for computer analysis on a solid state recorder. The electrode was calibrated at pH 1 and pH 7 before use. Appreciable gastro-oesophageal reflux was present when oesophageal pH was less than 4 for more than 5% of a 24 hour period. Endoscopy was performed using an Olympus XP paediatric gastroscope.

Oesophageal motility was assessed by a continuous perfusion manometric technique. After a four hour fast and sedation with chlorpromazine (1 mg/kg) a triple lumen polyvinyl catheter (outside diameter 3 mm), with side holes 4 cm apart and a distal Dent sleeve,[3] was positioned fluoroscopically in the oesophagus with the Dent sleeve straddling the lower oesophageal sphincter. In vitro tests on the three transducers before use showed a pressure rise of 53·4 kPa/second in response to sudden occlusion of the three recording orifices. The catheter was constantly perfused (1 ml/minute) with sterile water by a low compliance hydraulic capillary infusion system (Arndorfer Medical Specialties) and the proximal ends connected to three Hewlett-Packard pressure transducers (HP 1280 C) linked to an amplifier and chart recorder (HP 7754 B system). Pressure recordings were made from three levels: the proximal and midoesophageal body and the lower oesophageal sphincter, each separated by 4 cm (fig 1). The system was calibrated externally against a column of water and running speed was 100 mm/minute. Lower oesophageal sphincter pressure was measured taking atmospheric pressure as zero reference Peristalsis induced by a wet swallow was recorded and the following motility variables were derived from the manometric recording: amplitude of contractions (kPa), duration of contractions (seconds), and velocity of peristalsis (cm/second). The configuration of the oesophageal pressure wave was assessed and the presence of multipeaked contractions noted.

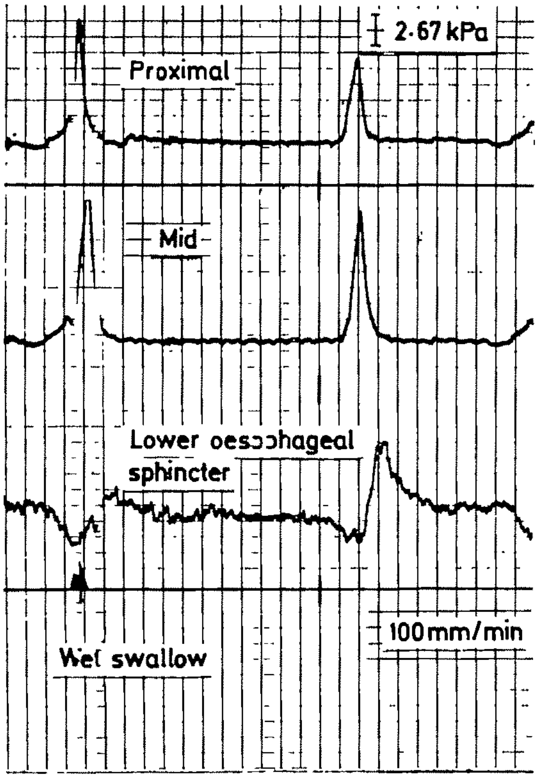

Fig 1 *Normal oesophageal peristalsis recorded in a control patient from the proximal and midoesophageal body and from the lower oesophageal sphincter*

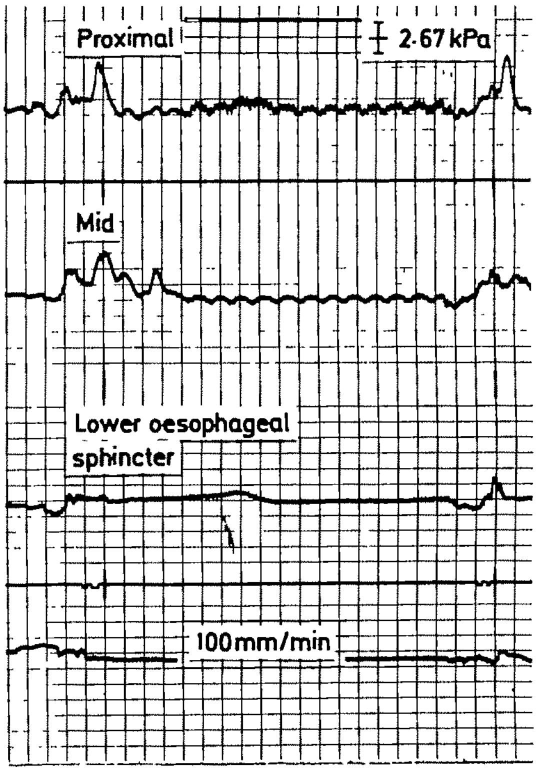

Fig 2 *Wet swallow induced peristalsis in a child with reflux oesophagitis showing low amplitude multipeaked peristaltic waves*

In the 15 patients with gastro-oesophageal reflux alone and the four patients with reflux oesophagitis, who had neurological abnormalities described above, combined oesophageal manometry and pH studies were performed. In these patients oesophageal manometry was performed as described above and, in addition, pH was recorded by attaching a small flexible pH electrode as used for 24 hour recordings 1 cm above the Dent sleeve of the manometric catheter and displaying the output of this electrode on the same polygraph as the manometric transducers. The pH electrode was calibrated in vitro at pH 1 and pH 7 before and after study. Gastro-oesophageal reflux was defined as a sudden drop in intraoesophageal pH below 4 for more than 10 seconds.

Relaxation of the lower oesophageal sphincter was considered to be synchronous when it occurred after a peristaltic sequence induced by swallow and asynchronous when it occurred independently of a swallow. Peristaltic sequences were judged to be primary when preceded by swallowing and secondary when not preceded by swallowing.

All patients were studied in the supine position. Statistical analysis was performed on the data by Wilcoxon rank sum test for unpaired data The study was approved by the standing committee on ethical practice of the Hospital for Sick Children and informed consent obtained from the parents of the children.

Results

BODY OF THE OESOPHAGUS

Configuration of the oesophageal pressure wave and patterns of motility

In all patients primary peristalsis was the most frequent motor pattern seen. An example of a primary peristaltic sequence induced by a wet swallow is shown in a control patient in fig 1. In control patients and those with gastro-oesophageal reflux without oesophagitis the waveforms were sharp single peaks, which proceeded aborally down the oesophagus and at the lower oesophageal sphincter were preceded by clear relaxation of the sphincter. In the patients with oesophagitis the waveform of the contractions was bizarre: the contractions were widened and multipeaked of low amplitude (fig 2).

Secondary peristalsis in response to refluxed acid was seen both in patients with gastro-oesophageal reflux alone and in patients with reflux oesophagitis As judged by acid clearance, however, in reflux oesophagitis it was often ineffective (see below).

Maximum amplitude of contractions (kPa)

There was a progressive decrease in the mean (SD) normal amplitude of contractions recorded from 9·60 (2·13) kPa in controls to 6·80 (3·20) kPa in patients with gastro-oesophageal reflux alone and 2·00 (0·93) kPa in patients with reflux oesophagitis. (When the controls were compared with each study group, $p<0{\cdot}01$.)

Duration of contractions (seconds)

An increase in duration of contractions was observed in patients in both study groups compared with controls, but this was not significant. Mean (SD) values were 3·9 (1·0) seconds in controls, 4·3 (1·1) seconds in patients with gastro-oesophageal reflux alone, and 6·8 (2·5) seconds in patients with reflux oesophagitis.

Velocity of peristalsis (cm/second)

Mean (SD) velocity was similar in all patients: 2·9 (1·6) cm/second in controls, 2·9 (2·1) cm/second in patients with gastro-oesophageal reflux alone, and

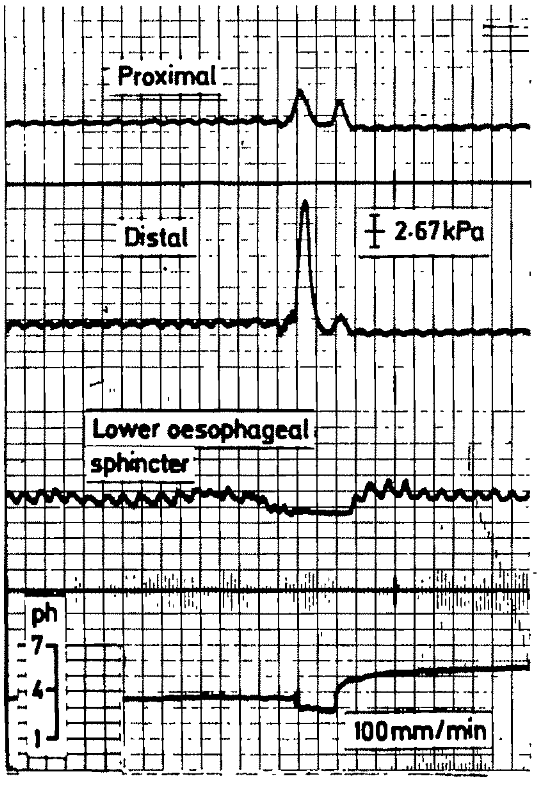

Fig 3 *Gastro-oesophageal reflux occurring synchronously with swallowing.*

2·3 (1·1) cm/second in patients with reflux oesophagitis.

LOWER OESOPHAGEAL SPHINCTER

Lower oesophageal sphincter pressure (kPa)

Mean (SD) lower oesophageal sphincter pressure was similar in controls and patients with gastro-oesophageal reflux alone (2·93 (0·53) kPa compared with 2·93 (1·6) kPa) but was significantly lower in patients with reflux oesophagitis (1·87 (0·93 kPa). (When the controls were compared with each study group, $p<0\cdot01$.)

Function of the lower oesophageal sphincter at time of reflux

A total of 122 episodes of reflux were recorded and analysed: of these 82 (67%) were synchronous with swallowing (as shown in fig 3) and 40 (33%) were asynchronous (as shown in fig 4). Fifteen patients with gastro-oesophageal reflux alone were studied. Of 98 refluxes 76 (78%) were synchronous and 22 (22%) asynchronous in this group. The episodes of asynchronous reflux all occurred in seven patients who had either recurrent respiratory problems or severe feeding disorders Mean (SD) clearance of refluxed acid was slower after asynchronous reflux than after synchronous reflux (2·0 (0·6) minutes compared with 0·6 (0·1) minutes, $p<0\cdot02$). In the four patients with oesophagitis, who were also the patients with neurological problems, 24 episodes of reflux were studied: 18 (75%) were asynchronous with swallowing and 6 (25%) were synchronous. In this group mean (SD) acid clearance was even slower after asynchronous reflux (4·5 (0·9) minutes compared with 0·6 (0·1) minutes, $p<0\cdot01$).

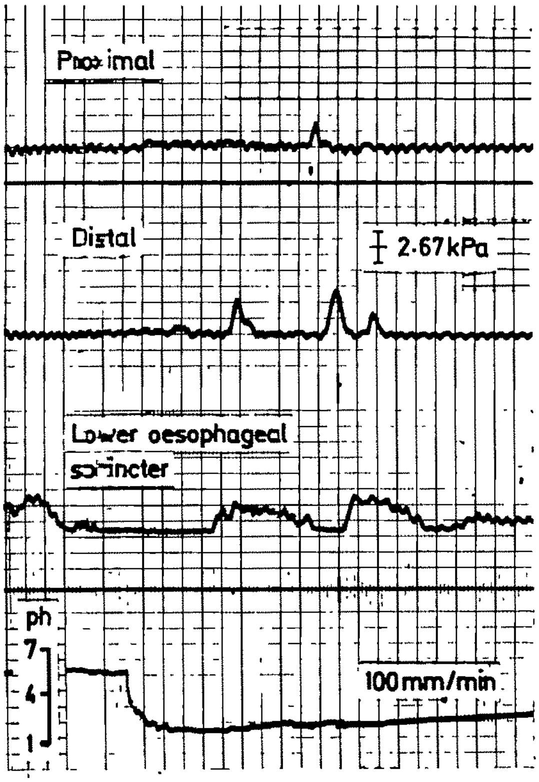

Fig 4 *Gastro-oesophageal reflux occurring asynchronously with swallowing resulting in a prolonged reduction of oesophageal pH and ineffective secondary peristalsis.*

Discussion

The data from this study provide evidence of the nature of disordered motor activity in patients with gastro-oesophageal reflux and show that a variety of pathophysiological mechanisms may operate. Oesophageal motor function was more disturbed in those with both gastro-oesophageal reflux and reflux oesophagitis than gastro-oesophageal reflux alone. Amplitude of contractions and lower oesophageal sphincter pressures were significantly lower than controls and often bizarre in nature; these findings are similar to those noted in previous studies.[4 5] In the patients with gastro-oesophageal reflux alone, however, we found no significant differences in oesophageal peristalsis and lower oesophageal sphincter pressure from the control patients.

Most (78%) of the episodes of reflux that we observed in children with gastro-oesophageal reflux alone occurred synchronously with swallowing, whereas in patients with reflux oesophagitis most reflux episodes (75%) were caused by relaxation of the lower oesophageal sphincter, which occurred asynchronously with swallowing. These findings are in accord with those of Baldi *et al.*[6] Secondary peristalsis occurred very promptly in the patients in whom reflux occurred synchronously with swallowing (as shown in fig 3) resulting in a short lived episode of acid reflux, which was rapidly cleared In those patients in whom reflux occurred asynchronously with swallowing acid clearance was much slower, being slowest in those with reflux oesophagitis, and secondary peristalsis was ineffective In this latter group the pH only slowly increased suggesting that the mechanism of return to normal pH was not clearance but perhaps buffering by swallowed saliva. Thus secondary peristalsis associated with reflux synchronous with swallowing was more effective in clearing acid than secondary peristalsis that occurred after asynchronous reflux.

We also attempted to examine the effects of endogenous acid exposure on oesophageal motility.

In those patients with reflux synchronous with swallowing refluxed acid was cleared promptly and induced a secondary peristaltic sequence, but those with asynchronous reflux had slower acid clearance and ineffective secondary peristalsis. Furthermore in the patients with reflux oesophagitis who had the slowest acid clearance bizarre multipeaked low amplitude waveforms were seen, and reflux asynchronous with swallowing occurred more often. It could be argued that both of these events result solely from the inflammatory response to prolonged acid exposure or that in addition there is an underlying motor abnormality, which results in less effective acid clearance. It is not completely clear from the present study which is the case as our study is cross sectional.

Our findings of reduced amplitude of smooth muscle contractions and bizarre multipeaked waveforms are similar to those previously reported.[7] We found in our previous studies in other regions of the gut that reduced amplitude of smooth muscle contractions is found in myopathic forms of intestinal pseudo-obstruction[8], we also found bizarre waveforms with disturbed propagation in various neuropathic forms of intestinal pseudo-obstruction.[9] It is possible that the disturbed motility observed in the patients with oesophagitis is simply as a consequence of the smooth muscle and oesophageal innervation operating in the environment of the inflammatory response to prolonged acid exposure. Some support for this hypothesis is provided by one study in which most children with oesophagitis and similar abnormalities to those reported here had their abnormal motor activity return to normal on resolution of the oesophagitis.[10] Previous studies in adults, however, have shown that the abnormal motor events antedated the oesophagitis.[11] In our patients with oesophagitis four suffered from neurological disease and these patients had the lowest lower oesophageal sphincter pressures and severely abnormal motility, and we have previously reported a series of children with brain stem tumours with severe reflux [12]

Thus in patients with gastro-oesophageal reflux and more serious related disorders reflux was associated with severe disturbance of oesophageal motor activity in which not only was the contractile activity and control of the lower oesophageal sphincter impaired—that is, asynchronous or inappropriate relaxation of a poorly contracting sphincter occurred—but also peristaltic activity to remove refluxed acid was impaired and less effective In patients with gastro-oesophageal reflux alone no such abnormalities could be detected and the cause of the reflux synchronous with swallowing that occurred was unclear, but it appeared to be very similar, but more frequent, to that which occurs physiologically on eating.[13]

The data from this study show that a variety of pathophysiological mechanisms may result in gastro-oesophageal reflux. Decreased basal lower oesophageal sphincter pressure was an uncommon cause of gastro-oesophageal reflux and only occurred in reflux oesophagitis. In this group, however, reflux was more closely related to relaxation of the lower oesophageal sphincter, which occurred asynchronously with swallowing, rather than to reduced lower oesophageal sphincter pressure. Prolonged exposure of the oesophagus to acid resulting in inflammation may lead to a vicious circle being set up with further deterioration of oesophageal motor activity and even worse acid clearance

Children with gastro-oesophageal reflux and trivial symptoms had gastro-oesophageal reflux synchronous with swallowing, and acid clearance occurred much faster than in those with serious symptoms. We suggest that reflux in those with gastro-oesophageal reflux alone is an exaggerated physiological response and may be treated by simple measures such as positioning and thickening of feeds, whereas in those with serious symptoms reflux may be related to intrinsic pathology of the oesophageal motor apparatus and require, in addition, the use of gastrointestinal prokinetic agents or, if these fail, surgery

MJM is grateful to Janssen Pharmaceutical Ltd, for their generous financial support

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Accepted 25 April 1988

Archives of Disease in Childhood, 1988, **63**, 1339–1340

What happens to the pylorus after pyloromyotomy?

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SUMMARY The rate of return to normal of the pylorus muscle in infantile hypertrophic pyloric stenosis was measured by ultrasound, using a simple pyloric volume calculation and a pyloric muscle index. The muscle hypertrophy took from two to 12 weeks to resolve.

First performed in 1911,[1] Ramstedt's pyloromyotomy has long been the standard treatment for infantile hypertrophic pyloric stenosis. Its success has left knowledge of what happens to the hypertrophied pyloric muscle dependent on measurements taken after the increasingly rare deaths and occasional later laparotomies.[2] These have shown that the pylorus eventually returns to normal leaving only a hairline longitudinal scar, and when combined with an earlier ultrasound study[1 3] have suggested that the pyloric muscle returns to normal within two to six weeks of the operation.

Ultrasound identification of pyloric hypertrophy started in 1977.[4] The basic technique is simple but the interpretation of the results has been complicated by the overlap of the upper limit of normal and the lower limit accepted as indicating muscle hypertrophy (fig 1).[5] This overlap also affects the interpretation of postoperative changes.

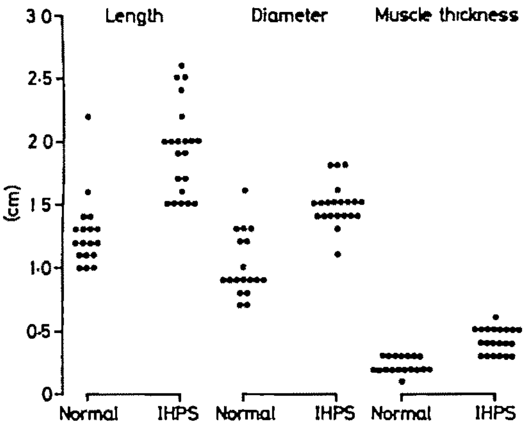

Fig 1 *Measurements of the pylorus in infantile hypertrophic pyloric stenosis (IHPS) and in normal controls.*

Patients and methods

Twenty five babies with a diagnosis of infantile hypertrophic pyloric stenosis confirmed at operation and 24 controls were studied. The protocol was approved by the local ethical committee and informed consent obtained for each child. The only reason for exclusion of a child from the study was a home too far from hospital to return easily for the additional ultrasound scans.

Initially the pyloric muscle was studied preoperatively and at two, four, and six weeks postoperatively. It was soon obvious that this was not a long enough follow up period and further measurements were taken at eight, 10, 12, and 14 weeks. Finally, follow up studies were restricted to before, and six and 12 weeks after the operation

Criteria for the ultrasound diagnosis of infantile hypertrophic pyloric stenosis had first to be established.[5] The pylorus was assumed to be a hollow cylinder. Its muscle volume was calculated from the formula $\pi TL(D-T)$ where T is the thickness, L the length, and D the diameter of the pylorus in cm. The accuracy of the ultrasound measurements was checked in the operating theatre for affected babies. This volume showed an overlap between cases and controls (normal range, 0·26–1·96 cm^3; babies with infantile hypertrophic pyloric stenosis, 1·50–4·90 cm^3) When the volume was divided by the weight of the baby in kg, a muscle index was obtained, which gave a complete statistical separation (normal range, 0·08–0·28; babies with infantile hypertrophic pyloric stenosis, 0·46–1·26) (fig 2). Weight loss increases the pyloric muscle index and one very marasmic infant without infantile hypertrophic pyloric stenosis measured at a postmortem examination had a value in the range for the affected babies. In a series of five cases and four controls, the validity of correcting for baby size was checked by dividing the volume by the baby's surface area (m^2),

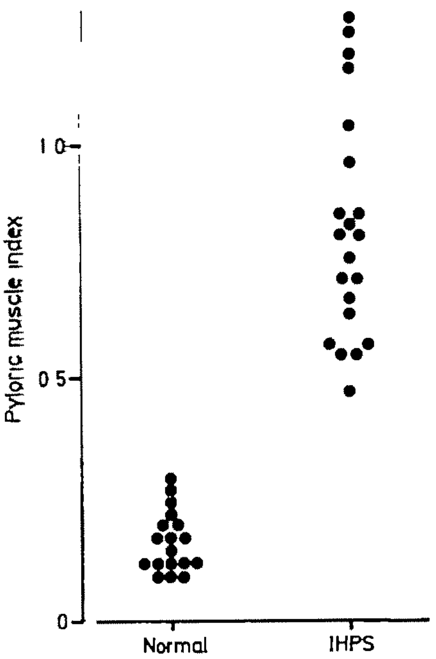

Fig 2 *Pyloric muscle index in infantile hypertrophic pyloric stenosis (IHPS) and in normal controls. Pyloric muscle index=pyloric muscle volume divided by body weight (kg).*

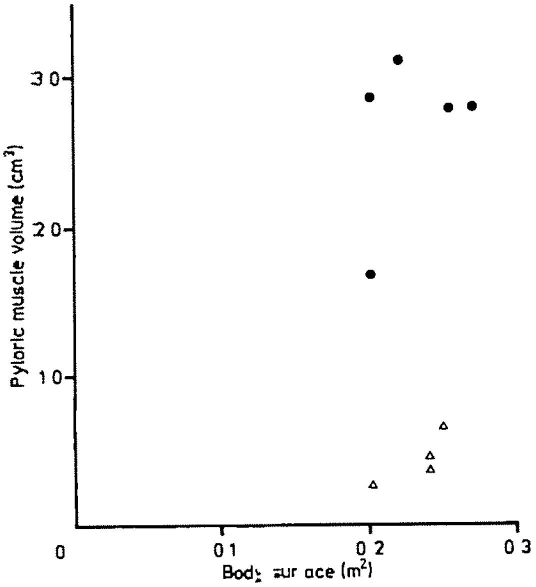

Fig 3 *Pyloric muscle volume divided by body surface infantile hypertrophic pyloric stenosis (●) and normal controls (△).*

which was obtained from the nomogram derived from the formula of Du Bois and Du Bois (fig 3).[6] This also gave a good separation, confirming the acceptability of the method and that failure to thrive was not a major feature of infantile hypertrophic pyloric stenosis in our series.

Results

The time to return to a normal pyloric muscle volume and to a normal pyloric index was measured using the control values as a normal base line. The pyloric muscle volume returned to normal in six weeks in six babies, but took 12 weeks in three of the last nine patients. If the pylorus is growing with the baby it will not return to the preoperative size. We have therefore used the muscle index, which takes this into account, to assess progress. Fig 4

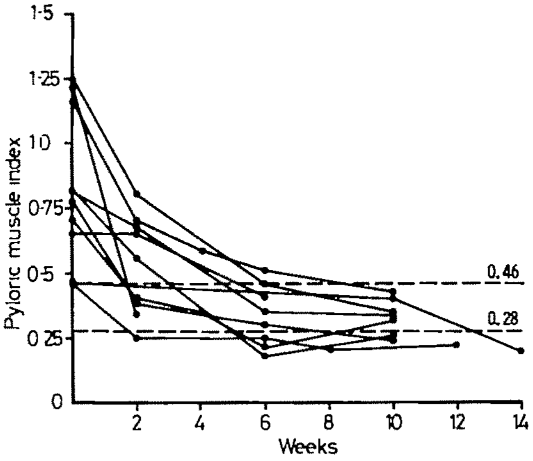

Fig 4 *Changes in pyloric muscle index after pyloromyotomy.*

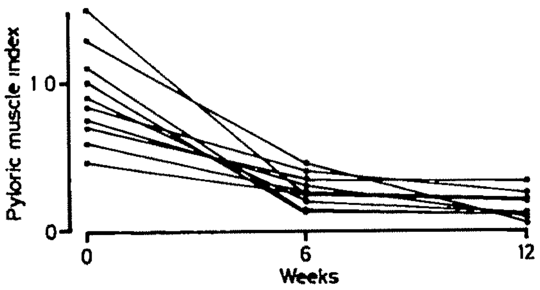

Fig 5 *Pyloric muscle index preoperatively, and at six and 12 weeks postoperatively.*

Table *Changes in pyloric muscle index after pyloromyotomy*

	Day of operation	*Time postoperative (weeks)*						
		2	*4*	*6*	*8*	*10*	*12*	*14*
No of patients	25	19	11	17	3	12	8	6
No (%) of patients with index								
≤0·46*	0	10 (53)	8 (73)	15 (88)	3 (100)	12 (100)	8 (100)	6 (100)
≤0·28†	0	4 (21)	4 (36)	8 (47)	3 (100)	7 (58)	8 (100)	6 (100)

*Diagnostic of pyloric stenosis, †normal (non-pyloric stenosis).

shows the pattern for 10 of the first 20 patients and fig 5 the simplified pattern, taking measurements preoperatively, and at six and 12 weeks. The table records the progress of all patients showing that the index falls below the lower limit for the diagnosis of infantile hypertrophic pyloric stenosis by 8 weeks, but takes 12 weeks to fall to the normal range.

Discussion

The pattern suggests that two processes are occurring simultaneously: the muscle bulk is reducing and the child is growing. The hypertrophy regresses at a variable rate but a normal size is consistently reached by 12 weeks postoperatively.

We wish to thank Mrs Jones, research secretary, for typing the paper and Mrs A Allen, senior I radiographer, for carrying out the ultrasound scans

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Accepted 6 May 1988

Archives of Disease in Childhood, 1988, **63,** 1342–1346

Penicillin allergy—a rare paediatric condition?

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SUMMARY A total of 298 children with a history of adverse reactions in connection with oral penicillin treatment were investigated with a radioallergosorbent test for penicillin metabolites, the skin prick test, and oral challenge with penicillin V. No severe reactions were seen. In 30 (10%) of the subjects slight to moderate skin reactions were observed on the seventh to 10th day of the challenge period. Between one to four years after the oral challenge 222 children were reinvestigated by interview. One hundred and ten had been given treatment by penicillin and 103 (94%) of these children tolerated the new treatment well and without any adverse reactions.

We conclude that the term 'penicillin allergy' is often misused. Such a diagnosis should be established by clinical investigation.

During early childhood oral treatment with penicillin is common and cutaneous reactions and gastrointestinal symptoms are not uncommon in connection with antibiotic treatment.[1] Many children who react in this way are considered allergic to penicillin, and for fear of severe reactions the treatment is usually stopped. Subsequently, in many cases an alternative treatment with erythromycin, cephalosporin, or trimethoprim-sulphamethoxazole is given. None of these drugs, however, can be regarded as the primary drug of choice in the treament of respiratory tract infections in children. Erythromycin is rarely considered to produce any allergic reactions[2]; however, frequent use of it has created resistant Gram positive coccus strains, and its efficacy against *Haemophilus influenzae* infections in children has been reported to be limited.[3] Cephalosporins are reported to cause an increase in the frequency of side effects[4 5] and a cross reactivity with penicillin exists.[6 7] Trimethoprim-sulpha-methoxazole may give rise to undesirable side effects, immunological reactions, and bone marrow depression. These adverse effects have most often been reported in adults.[8] Thus penicillin still seems to be the first line antibiotic.

Side effects after treatment with penicillin are seldom IgE mediated,[9 10] and severe reactions are very rare in childhood.[11 12] The diagnosis of penicillin allergy cannot be established without thorough investigation.

The aim of this prospective study was to study the possibility of identifying or excluding 'penicillin allergy' in children who had a history of adverse reactions in connection with prior oral penicillin treatment by means of a radioallergosorbent test, the skin prick test, and oral challenge and to determine whether the diagnosis of 'penicillin allergy' is overused.

Subjects and methods

A total of 298 children, 1–15 years old (median age 3 years) with a history of side effects in connection with prior oral penicillin treatment were investigated. They were all outpatients in the Sachs' Children's Hospital or the paediatric department of Huddinge Hospital during the period 1982–5 and all tests were performed using routine procedures.

Most children were investigated within six months of the suspected side effect. A careful history of the adverse reaction was obtained and, where possible, the facts were compared with previous medical records.

Specific IgE to the penicillin metabolites, penicilloyl V and G, was determined with the radioallergosorbent test (Phadebas RAST) in 277 children following the recommendations of the manufacturer. In 22 children the reaction had taken place more than six months previously, therefore no test was performed. In these patients the titres for the test may have decreased and they were not therefore regarded as reliable.

Skin prick tests on the forearm, using benzylpenicillin (0·06 g/ml) and phenoxymethylpenicillin (0·05 g/ml), were made in all patients using saline and histamine (1 mg/ml) as negative and positive controls respectively. A weal larger than 2 mm was considered to be positive.

Oral challenge was performed with phenoxymethylpenicillin in 297 patients when there was no clinical evidence of infection. The challenge dose with a suspension or tablets was set at 25 mg/kg body weight twice a day for 10 days. The first one or two doses were given in the hospital and the patient was observed in the office for two hours. After the 10 day oral challenge period the patients filled in a questionnaire concerning symptoms during the penicillin challenge. If any side effects of importance occurred, the patient was seen at the office after three weeks and in relevant cases a new radioallergosorbent test was performed

FOLLOW UP

In order to evaluate the impact of the penicillin allergy testing and the later antibiotic treatment a follow up investigation was made one to four years after the oral challenge test. A questionnaire was given to those 234 patients who had been subjected to challenge more than one year earlier; 222 families (95%) answered it.

Results

A heredity to atopic disease was present in 137 (46%) of the children. At the time of the initial adverse reaction 225 (76%) were less than 7 years of age (table 1). A total of 185 (62%) of the children had been treated with phenoxymethylpenicillin, 75 (25%) with amoxycillin/ampicillin, and 39 (13%) with cephalosporins, erythromycin, or other unstated preparations. In a third of the children the main symptom was an exanthem without pruritus and 168 (56%) had an exanthem with pruritus or urticaria, in some cases in conjunction with facial oedema or swollen joints (table 2). No asthmatic or anaphylactic reactions were reported. The time when the side effect occurred was mainly between day zero to day three or after one week of treatment (table 3). Skin prick tests were negative in all 298 children.

Table 1 *Age distribution in 298 children with adverse reactions during treatment with penicillin and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Age group (years)	*No of children*	*No (%) with positive challenge*
0–<4	151	8 (5)
≥4–<7	74	10 (14)
≥7–≤10	29	4 (14)
>10	27	7 (26)
Unknown	17	1 (6)

Radioallergosorbent tests for penicillin metabolites were negative in 274 of the 277 tested cases. In three children increased titres were found. One of these had a high IgE value as well as IgE antibodies to human serum albumin. The titre in this child was therefore regarded as non-specific. One child showed a borderline value. The third child had a high titre without a high IgE value. This patient was the only one in whom no oral challenge was done.

Of the 297 children who were given phenoxymethylpenicillin as a challenge 30 (10%) showed clinical reactions, mainly with symptoms such as urticaria, an exanthem with pruritus and, in some cases, with oedema of the face and joints. No serious reactions or anaphylaxes were seen. In 22 of 30 cases the reactions occurred on the seventh day of challenge or later. The challenge test was positive in 19 (21%) of children who had a primary reaction on the seventh day, or later, as compared with five (4%) of children who had a primary reaction during the first three days (table 3). No child with exanthem alone reacted again whereas 14 (11%) of the children with urticaria or pruritus, or both, did.

Table 2 *Type of adverse reaction during treatment with penicillin in 298 children and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Type of reaction	*No of children*	*No (%) with positive challenge*
Exanthem—no pruritus	99	0
Urticaria—pruritus	132	14 (11)
Urticaria and swollen joints and/or facial oedema	36	15 (42)
Other symptoms	31	1 (3)
Anaphylaxis	0	—

Table 3 *Time after treatment with penicillin and development of side effects in 298 children and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Time for reaction (years)	*No of children*	*No (%) with positive challenge*
Day 0–3	131	5 (4)
Day 4–6	46	4 (9)
Day 7+	90	19 (21)
Unknown	31	2 (7)

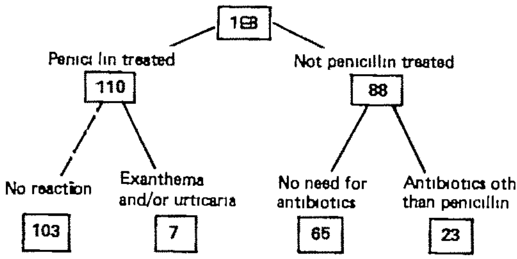

Figure *Follow up investigation in 198 cases one to four years after a negative oral challenge test with phenoxymethylpenicillin.*

Of the children with urticaria associated with swollen joints or slight facial oedema, or both, 15 (42%) reacted on challenge (table 2). Below 3 years of age only eight (5%) of the children reacted on challenge, while seven (26%) of those above 10 years of age had a reaction (table 1). The child with a borderline titre on the radioallergosorbent test developed only a mild urticaria on the seventh day after an phenoxymethylpenicillin challenge. A new radioallergosorbent test was performed in 13 of 30 children who reacted to the oral challenge and 12 still had low values. In the group with a positive heredity 15 (12%) had a reaction as compared with 13 (8%) in the group with a negative heredity for allergic diseases.

Two hundred and twenty two children were investigated using a questionnaire one to four years after the oral challenge test in order to ascertain whether side effects to penicillin treatment given for infections had occurred after the challenge. Half of the subjects (110) received penicillin again and 103 (94%) showed no side effects. Seven reacted with cutaneous manifestations, such as exanthem or urticaria (figure). All these reactions occurred on the 7th–10th days of treatment or after the end of the treatment. Furthermore one child who had a positive penicillin challenge test had no reaction later when accidentally treated with penicillin. Two of the seven children who, according to the questionnaire had reacted, were rechallenged during an infection free period and did not react on this occasion.

A total of 88 children with a negative oral challenge had not received further penicillin treatment (figure). In 65 cases there had been no need for penicillin, but in 23 cases the children had been treated with erythromycin, cephalosporin, or trimethoprim-sulphamethoxazole, partly because of concern that phenoxymethylpenicillin might cause severe reactions. This means that 17% of those children who might have needed penicillin (110+23) did not receive adequate treatment, despite a thorough investigation.

Discussion

This study has shown that in 298 consecutively investigated children diagnosed as allergic to penicillin a type 1 reaction to penicillin was not confirmed in 297 cases by oral challenge. One child with an increased titre on a radioallergosorbent test was not challenged for ethical reasons. These findings accord with the results of an earlier report where oral challenge was performed in 219 cases for 10 days.[11] Furthermore, the present study has shown that the results have been reliable up to four years after the investigation. Ninety four per cent of the children who had been treated with penicillin after the oral challenge showed no side effects. Only 6% had cutaneous manifestations, such as mild urticaria or an exanthem, or both, and they all occurred after the seventh day of treatment. No cases of anaphylaxis or other severe reactions were seen.

Children reacting in connection with ampicillin and cephalosporin treatment were included in the study because these compounds all belong to the β lactam group of antibiotics. Furthermore, the allergenic metabolites that can give rise to IgE mediated reactions are the same for ampicillins and penicillin V and there exists cross reactivity between cephalosporins and phenoxymethylpenicillin. Erythromycin is chemically different from the penicillins but the two children reacting on erythromycin had reacted earlier in the same way in connection with phenoxymethylpenicillin treatment and were thus included in the study.

As most children studied were below 6 years of age some reactions may be due to additives in the syrup preparations. It has not been possible to differentiate between side effects of penicillin per se and of the additives.

Metabolites of penicillin can act as allergens and after sensitisation, IgE mediated reactions may be elicited.[9] [10] Type 1 allergy reactions are rare and may be caused by both major and minor determinants of penicillin metabolites. The radioallergosorbent test in its present form can only identify reactions due to major determinants and it must therefore be considered of limited value in the diagnosis of penicillin allergy. It should also be kept in mind that falsely increased titres also occur, especially when IgE concentrations are high. Increased titres may decrease with time, giving false negative results after several months.

Skin prick tests, such as those performed in this study, are of limited value; if used, they should be combined with intradermal testing, as described by others.[11-13] Here too the use of both major and minor determinants is preferable.[14] Unfortunately, minor determinants are not commercially available for diagnostic purposes.

Today, the only reliable tool for identifying true penicillin allergy is probably oral challenge. If the purpose is to identify IgE mediated reactions it is not necessary to perform prolonged oral challenge. The type 1 reaction appears after the first dose. Later reactions should be regarded as expressions of other underlying mechanisms.

In most children who have had symptoms in connection with treatment with oral penicillin the side effects are minor and the children can continue taking penicillin as prescribed. There are no contraindications for future penicillin treatment in connection with infections. The tendency to react to repeated courses of penicillin treatment seems to be influenced by factors such as age, type of reaction, and the time of the primary reaction during penicillin treatment. A heredity of allergic diseases does not seem to be of importance.

Severe reactions with symptoms of anaphylaxis, asthma, or Stevens-Johnson's syndrome are extremely rare, but in such cases the treatment should be stopped and the child should not be given penicillin again.

Urticaria, pruritus, and oedema of the joints and face are not uncommon side effects, especially not at the end of the treatment. In these cases type 1 allergic mechanisms are not involved. It may be advisable to interrupt the treatment, however, and to investigate the patient later with skin testing and oral challenge when no infection is present.

It may be concluded that the diagnosis of penicillin allergy in connection with treatment with oral penicillin in childhood is often over used and that a thorough investigation must be done before the diagnosis can be established.

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Accepted 3 May 1988

Commentary

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Most 'drug reactions' are diagnosed on presumption: the patient's history and their previous experiences; probabilities concerning the reputation of the medicine; and timing of its administration in a particular instance. With the penicillins the rashes are a prominent feature; the commonest are urticarial, perhaps even with blistering and some are vasculitic (measles like) perhaps with purpura A general scarlet fever like diffuse reddening without lymphadenopathy, but with a later 'branny desquamation', may be seen and less commonly an eczematous, itchy rash with widespread scaling early in the efflorescence. Scaliness may also follow the more obviously vasculitic rashes while urticaria on microscopical examination may prove to show definite vasculitis.

As a student, I clerked a patient who died of pencillin anaphylaxis catastrophically suddenly; he had perished before the houseman and his clerk got to the bedside. In 33 years of practice I have seldom prescribed penicillin. But fatal anaphylactic shock is exceptionally rare with oral penicillin. Serum sickness is commoner and much more drawn out in its development—urticaria, pains in belly and joints, distressed breathing, and fainting. The urticaria may persist for months, waxing and waning. Recurrence of urticaria for which no cause is discovered, may be guessed to be due to exposure to minute quantities of penicillin or similar cross reacting substances in the diet or as aerosol. 'Side effects' of penicillin administration should be read as 'ill effects'.

Skin testing with the 'major determinant', the penicilloyl polylysine nucleus, and the 'minor determinants' had its time but the vogue has passed because it never was satisfactory and seldom expedient.

This paper evaluates a blood test, the fairly expensive radioallergosorbent test. If this were to be developed to be entirely reliable as a predictor of all penicillin allergy, then much of the mythology and speculation would be replaced by sound knowledge. At the moment, only allergy to the penicillin nucleus and not to the 'soup' of various and variable chemicals that are lumped together as 'minor determinants can be accounted for. Risky rechallenge using the same penicillin or one that might be expected to cross react in patients with suspected allergy to satisfy academic or practical purposes would then be obsolete.

The precision of this paper is blurred by the inclusion of ampicillin, always considered by dermatologists to be a special case in which accidental rechallenges have long been noted to fail to produce the characteristic vasculitic or morbilliform eruption. Maybe the rash derives from destruction products of the 'bug' and not the 'drug'? The inclusion of cephalosporin and most particularly, erythromycin would not seem to be appropriate whereas the cloxacillins are cross reactive presumably through truly allergic mechanisms.

For the moment, if parent or child believes he is 'penicillin sensitive', I consider it bad doctor-patient practice to ignore their assessment of their observations and prudent to use an alternative antibiotic. So many doctors have their reputations besmirched for not listening to their patients and antibiotic prescribing has been the centre of so many of these conflicts.

Archives of Disease in Childhood, 1988, **63,** 1347–1352

Maturation of corticospinal tracts assessed by electromagnetic stimulation of the motor cortex

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SUMMARY The motor cortex can be excited in adults using electromagnetic stimulation, and the latency to the evoked muscle action potential allows an assessment of the integrity of corticospinal tracts. We applied this technique in children to describe the maturation of corticospinal tracts. The latency from cortical stimulation to the onset of the evoked muscle action potentials and the subject's height were recorded. The subject's height was divided by the latency to the onset of the evoked muscle action potential to provide an index of the conduction velocity within descending motor pathways (V_I). It is possible to evoke muscle action potentials after electromagnetic stimulation of the motor cortex in children including preterm babies and there is a stepwise increase in the sensitivity to stimulation between 8 and 11 years of age. In addition there is a progressive increase in V_I with age; adult values are attained at about 11 years.

The successful application of this technique in children suggests that electromagnetic stimulation of the motor cortex has the potential to allow detection of abnormality in motor pathways in newborn babies and young children.

In young children it is difficult to assess the integrity of central motor pathways. Clinical examination is unreliable particularly in the very young child or in the newborn infant.[1] The recent development of the technique of electromagnetic stimulation of the motor cortex provides, for the first time, the opportunity to assess objectively the integrity of corticospinal tracts in children.[2] This method uses a flat circular stimulating coil through which a brief current is passed.[2] The pulsed magnetic field so generated induces electrical currents in the brain, which are assumed to excite the superficial layers of the cortex. When the coil is held over the motor cortex, activity is evoked in the corticospinal tracts and results in muscle action potentials, measureable by surface electromyogram electrodes.[2 3] The method is simple, painless, and quick and is therefore particularly suitable for use in children. Before this technique can be used to investigate abnormalities in motor pathway function in children, however, the normal developmental changes in the conduction velocity within the motor pathways need to be defined.

The aim of this study was, therefore, to define the change with age in the conduction velocity in descending motor pathways after electromagnetic stimulation of the motor cortex in healthy subjects.

Subjects and methods

This study obtained the approval of the Newcastle Health Authority ethical committee after the evaluation of the safety of the technique in an animal model.[4] We studied 142 subjects who ranged in age from 33 weeks' gestation to 50 years; they were healthy with no history or clinical signs of a neurological disorder. Informed consent was obtained from subjects aged greater than 16 years and from the parents of children aged less than 16 years.

To record muscle action potentials, skin mounted electromyogram electrodes were placed over the right abductor digiti minimi in all subjects older than 6 months of age; in those aged less than 6 months the muscle action potential was recorded from the right biceps brachii. The electromyogram was amplified by 10^4 by a Nicolet Physiological amplifier (NIC-1001A) and filtered using a band pass of 5 Hz to 1·5 kHz. The amplifier was interfaced to a microcomputer for storage of the wave form and for subsequent analysis.

To stimulate the motor cortex, a high current low voltage magnetic stimulator[5] was used to generate a pulsed magnetic field of up to 1·9 tesla (T), with a rise time of 100 µs and total duration of 300 µs. The characteristics of the magnetic field generated are shown in fig 1. The stimulating coil was held tangential to the scalp and positioned to obtain the maximum muscle action potential in each subject.

The study protocol was to attempt to evoke muscle action potentials after electromagnetic stimulation of the cortex in relaxed abductor digiti minimi (or biceps brachii in those less than 6 months old). Merton and his colleagues have shown that the threshold for evoking muscle action potentials can be lowered if there is isometric contraction in the relevant muscle.[6] Therefore, if it was not possible to evoke a muscle action potential in relaxed muscle isometric contraction of the abductor digiti minimi in subjects older than 6 months was achieved by placing a weight in the palm of the outstretched and supinated right hand; in those aged less than 6 months reflexive isometric contraction in biceps brachii was induced by eliciting a traction reflex.[7]

The latency from cortical stimulation to the onset of the evoked muscle action potential was determined and the subject's standing height, or crown to heel length in those less than 1 year old, were recorded

Results

Representative recordings of evoked muscle action potentials after electromagnetic stimulation of the motor cortex in subjects aged 5 days, 5 years, 10 years, 16 years, and 23 years are shown in fig 2.

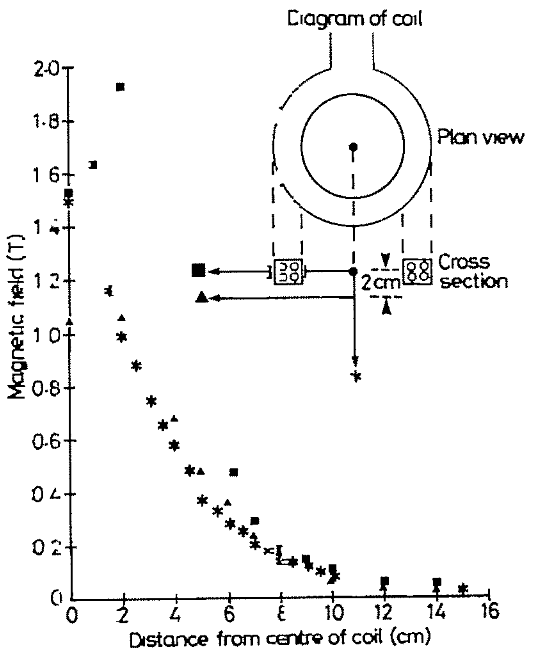

Fig 1 *Intensity of the magnetic field generated by the stimulating coil in three planes in relation to the centre of the coil*

Muscle action potentials were evoked in all 142 subjects; the facilitation of an isometric contraction was required in 71. The incidence of obtaining a evoked muscle action potential from relaxed muscle in relation to the subjects' ages is shown in fig 3. All the subjects aged less than 8 years required the facilitation of an isometric contraction. There was a stepwise increase in the incidence of obtaining muscle action potentials in relaxed muscle between the ages of 8 and 11 years but it was not until 20 years of age that muscle action potentials could be consistently obtained in relaxed muscle.

The mean (SD) latency to the evoked muscle action potential in subjects older than 20 years was 21 (1) ms. These data are consistent with those obtained in healthy adult subjects by previous

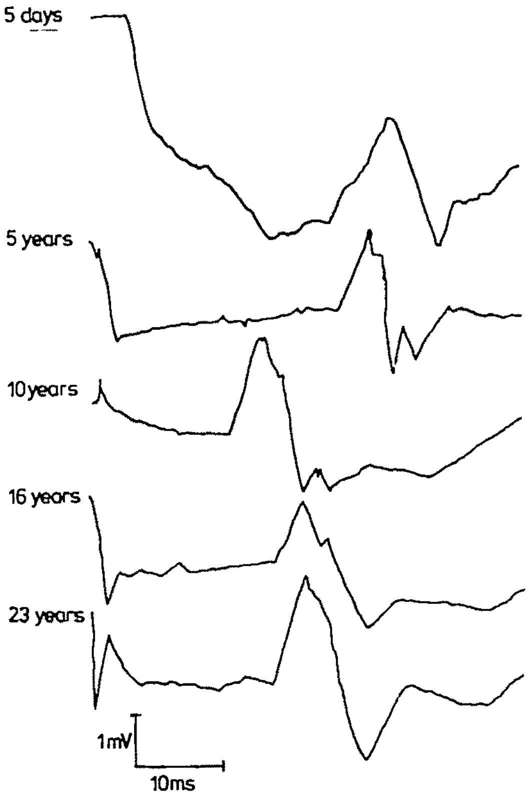

Fig 2 *Representative recordings of muscle action potentials evoked after electromagnetic stimulation of the motor cortex in subjects of differing ages The muscle action potential was recorded from abductor digiti minimi in all except the subject of 5 days of age where it was recorded from biceps brachii.*

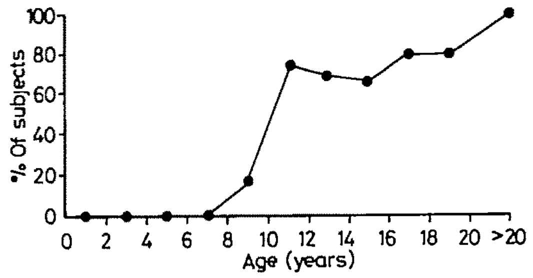

Fig 3 *Incidence of obtaining an evoked muscle action potential in the relaxed muscle in relation to age.*

workers.[2 3] There was a very wide variability in the latency to evoked muscle action potential in children. There was, however, a reduction in this latency with age from a mean (SD) of 31 (1·1) ms in term babies (fig 4).

The latency to the onset of a muscle action potential is dependent on the conduction velocity within the descending motor pathways and the distance travelled. It is not possible to measure accurately the distance from the motor cortex to a peripheral muscle in living subjects. To provide an estimate of this distance the subjects height or crown to heel length was used. An index of the

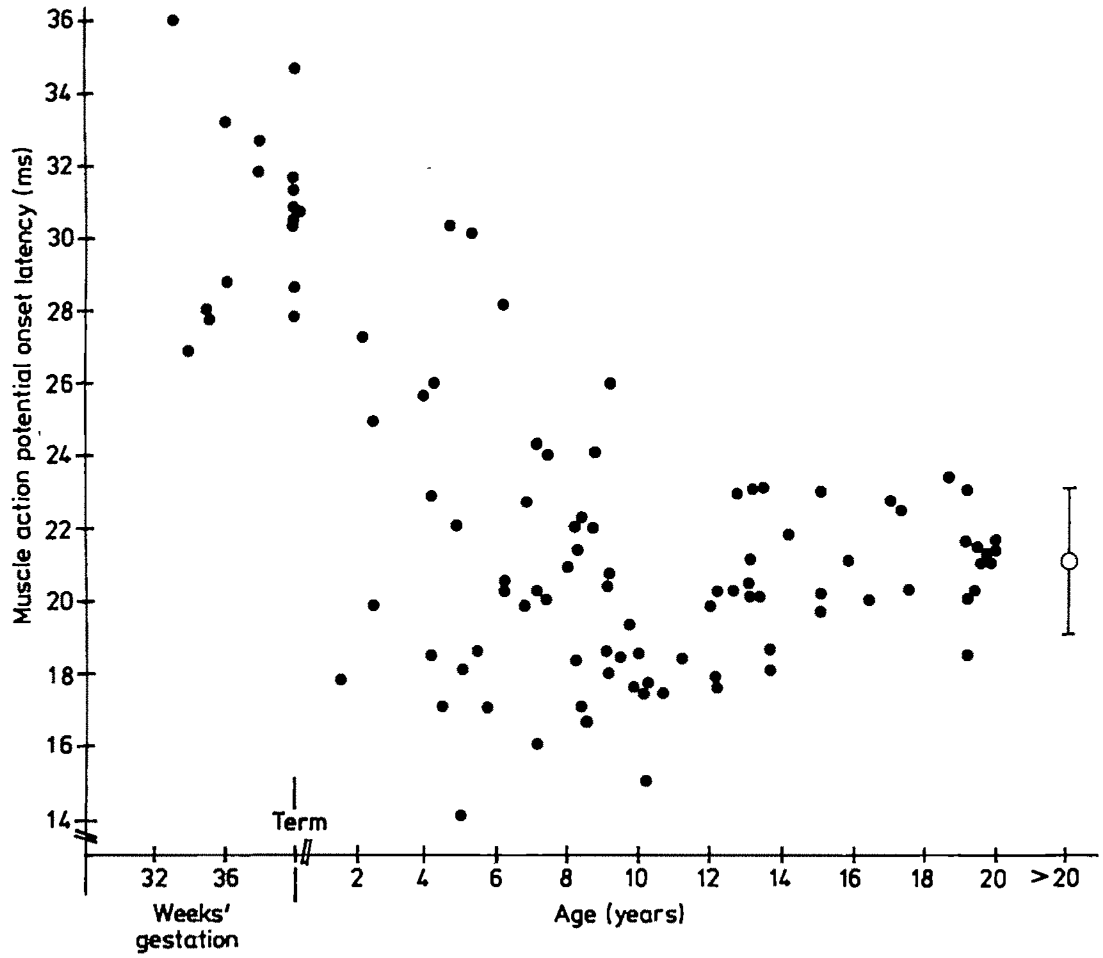

Fig 4 *Latency to the onset of an evoked muscle action potential in abductor digiti minimi in relation to age. The latency for the subjects less than 6 months is derived from the latency to biceps brachii plus the estimated conduction time from biceps brachii to abductor digiti minimi. The mean (2 SD) for the 30 subjects >20 years old is indicated on the right.*

conduction velocity in corticospinal tracts (V_I) was calculated by dividing the height or crown to heel length by the latency to the onset of the evoked muscle action potential. These data are shown in relation to the subject's age in years in fig 5. This shows a progressive increase in V_I with age from 10·5 m/s at 33 weeks' gestation until adult values (79 ± 10) m/s) are reached by the ages of 11 years.

Discussion

This study has shown for the first time that it is possible to evoke activity in descending motor pathways after electromagnetic stimulation of the motor cortex in premature and term newborn babies, infants, and older children.

Currently it is uncertain which neural elements in the motor cortex are excited by the stimulus.[8] There is evidence, however, to suggest that the electromagnetic stimulus excites interneurons in the motor cortex, resulting in indirect rather than direct activation of the pyramidal neurons.[9]

An unexpected finding in our present study was the need for an isometric contraction in order to evoke a muscle action potential after electromagnetic stimulation of the motor cortex in all children aged less than 8 years. This need for facilitation suggests that the cortical interneurons or pyramidal neurons have a higher threshold for activation in young children than in adults or that the alpha motor neurons are less readily excited by the activity evoked in the descending motor pathways after electromagnetic stimulation. The sudden increase in the incidence of obtaining a muscle action potential in relaxed muscle between the ages of 8 and 11 years further suggests that during this period there is a stepwise decrease in the threshold for the activation of cortical neurons or alpha motor neurons or both.

Bruce and Tatton, using microelectrical stimulation of the cortex in the kitten, have described a

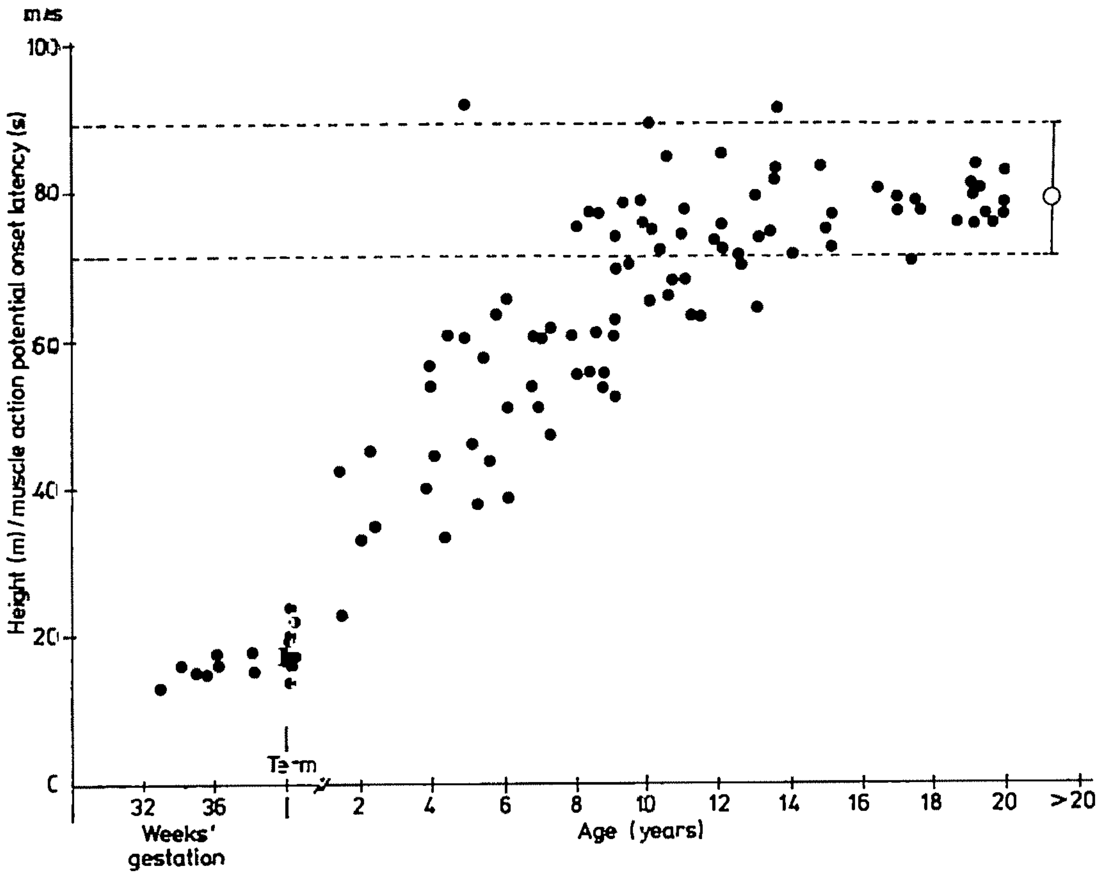

Fig 5 *Correlation of V_I (height or crown to heel length/latency to the onset of the evoked muscle action potential) with age*

stepwise change with age in the sensitivity of the neurons in the cortical motor area 4 to electrical stimulation.[10] These data suggest that at least part of the maturational change in threshold for evoking muscle action potentials observed may be cortical in origin.

At present most authors only consider the latency of the muscle action potential for determining normal and abnormal responses.[2 3 8] Our data show that it is also important to consider the threshold for evoking muscle action potential in defining both normal and abnormal responses.

In man the latency from cortical stimulation to evoked activity in the cervical spine is about 6 ms [8] This short latency suggests that the large myelinated axons of the corticospinal tract are concerned in the conduction of descending activity after electromagnetic stimulation of the motor cortex. This conclusion is supported by studies in primates in which short latency neural activity has been recorded in the lateral corticospinal tract after electromagnetic stimulation of the motor cortex.[9]

We have shown a progressive increase in the index of conduction velocity (V_I) within the descending motor pathways up until the age of 11 when adult values are achieved. It has been established that the conduction velocities in peripheral motor nerves reach adult values by 3 years.[11] Histochemical studies of postmortem material have shown that myelination of corticospinal tracts is complete by 3 years of age.[12] Our data suggest that there is an as yet uncharacterised process of maturation that leads to an apparent increase in the conduction velocity within the corticospinal tract beyond the completion of myelination. The decrease with age in the latency to the evoked muscle action potential may be due, in part, to the development and maturation of interneuronal synaptic connections both at the cortex and the spinal cord. This conclusion is supported by our finding of the change with age in the threshold for evoking muscle action potentials.

The normal development of motor behaviours has been studied in detail[13]; these studies have shown continued acquisition of fine motor skills up until the age of 8–10 years.[14] Our findings provide corresponding neurophysiological evidence of continuing maturation of central motor pathways up until the ages of 11 years.

Desmedt and his colleagues have studied the maturation of the conduction velocities within central somatosensory pathways.[15] These studies have shown a similar pattern of maturation with adult values being reached by 8 years of age.

Finally it has been shown in adults that prolongation of the latency to evoked muscle action potential after electromagnetic stimulation of the cortex is a sensitive indicator of abnormality in descending motor pathways.[2 3] The electromagnetic stimulation of the cortex was well tolerated by all the subjects in our study including the very young children and the newborn infants. The ease in the use of this technique in children suggests that it may provide an exciting opportunity for the objective assessment of motor pathway dysfunction in young children and in particular for the early detection of cerebral palsy in the newborn baby.

A study is presently being conducted to assess the sensitivity of this technique for the detection of upper motor neuron lesions in newborn infants and young children

We would like to thank the following for their support and help the subjects and their parents, Professor S Miller, Professor A Aynsley-Green, Dr D Milligan, Mr P Byrne, Mr P Oliver, Mr T Essex, and Mrs B Kenyon. Financial support is acknowledged from the Mason Medical Foundation and The Newcastle Health Authority THHG Koh is a Medical Research Council Training Fellow Dr J Eyre is a Wellcome Senior Fellow in Clinical Science

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Accepted 27 June 1988

Archives of Disease in Childhood, 1988, **63,** 1353–1358

Neural dysfunction during hypoglycaemia

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SUMMARY There is controversy over the definition of hypoglycaemia in neonates and children and over its significance when 'asymptomatic'. We measured sensory evoked potentials in relation to blood glucose concentration in 17 children: 13 were fasted or given insulin to investigate endocrine or metabolic abnormalities and four had spontaneous episodes of hypoglycaemia. Abnormal evoked potentials were recorded in 10 of the 11 children whose blood glucose concentration fell below 2·6 mmol/l; five of these 10 children were 'asymptomatic'. No change in evoked potentials was recorded in the six children whose blood glucose concentration remained above 2·6 mmol/l. Our findings suggest that the blood glucose concentration should be maintained above 2·6 mmol/l to ensure normal neural function in children irrespective of the presence or absence of abnormal clinical signs.

Glucose, like oxygen, is essential for normal brain cell function. It cannot now be disputed that hypoglycaemia causes brain damage or that effective management of hypoglycaemia protects from this neural damage.[1 2] Thus for example, in 1960 Haworth and Coodin found an incidence of 51% of severe mental retardation among 35 children who had had recurrent 'idiopathic' hypoglycaemia when aged less than 6 months.[3] In 1984, Soltesz *et al* in a review of the outcome of 18 children who had hyperinsulinaemic hypoglycaemia found that the incidence of severe mental retardation had been reduced to 15%.[4] They concluded that this improved outcome resulted from early identification, correct diagnosis, and effective management of the hypoglycaemia.

Although there is general agreement on the need to maintain blood glucose concentrations above a 'critical' level in young children and neonates there is no agreement among practising paediatricians and the major paediatric textbooks as to the lowest safe concentration of glucose.[5] This difficulty with the definition is understandable in view of the lack of reliable clinical signs when the blood glucose concentrations fall in newborn infants and young children, and in view of the continuing controversy over whether 'asymptomatic' hypoglycaemia causes neurological dysfunction and damage [6 7]

To resolve this controversy the lowest blood glucose concentration at which normal neural function is preserved needs to be determined by a correlation between objective measurements of neurophysiological function and blood glucose concentrations The aims of our study were therefore: (a) to use evoked potentials to measure objectively neural function in relation to blood glucose concentration and (b) to determine if there is a measurable difference in neural function between children who are 'symptomatic' and 'asymptomatic' during periods of low blood glucose concentrations.

Subjects and methods

This study formed part of a project to evaluate the use of evoked potentials in normal and sick newborn infants and children. Approval was obtained from the local health authority ethical committee and informed consent was obtained from the parents before each study.

Seventeen children were studied and were selected from two groups of children. The first group comprised children admitted for investigation of metabolic or endocrine disorders, these children were studied when their investigations included the provocation of hypoglycaemia by either fasting (n=11) or insulin administration (n=2). The second group consisted of children who had recurrent spontaneous episodes of hypoglycaemia (n=4).

In all subjects serial blood samples were obtained. An immediate bedside estimation of the whole blood glucose concentration was made using the Reflolux II device (BCL Ltd). Blood samples were obtained at 30 minute intervals while the blood glucose concentration was above 3 mmol/l and at 15 minute intervals if the blood glucose concentration fell below 3 mmol/l. After blood had been withdrawn for clinical diagnostic purposes normoglycaemia was restored by giving glucose or glucagon.

Venous blood was obtained from those subjects in whom an intravenous catheter had been sited, capillary blood was used in the other subjects. From each sample blood was added to fluoride coated tubes for later estimation of the blood glucose concentration using the glucose oxidase method[8] and to perchloric acid for the later estimation of the concentration of ketone bodies (3-hydroxybutyrate and acetoacetate) using enzymatic methods on a Cobas Bio Centrifugal Analyser (Roche) in fluorometric mode.[9]

In all subjects, brainstem auditory evoked potentials (n=12) or serial somatosensory evoked potentials (n=5) were recorded immediately after each sample of blood was taken. All the evoked potential recordings were made by one person (THHGK) who did not take part in the clinical management of the child during the study. The evoked potentials were recorded using a portable Nicolet CA1000 Clinical Averager at the patient's bedside.

Brainstem auditory evoked potentials were elicited using an alternating click (rate 33/s, duration 100 μs) delivered by a Nicolet TIP 10 click generating module. The intensity of the click was determined for each individual subject so that evoked potentials could be elicited reliably in the baseline recordings. The intensity of the stimulus then remained constant throughout each study. To record the evoked potential a silver/silver chloride cup electrode (8 mm in diameter) was placed centrally on the forehead and on the ipsilateral mastoid; an indifferent electrode was placed over the contralateral mastoid. The skin to electrode impedance was maintained at 3 kohms or less. The electroencephalogram was amplified using a Nicolet HGA 200A Physiological Amplifier with a band pass filter of 300–3000 Hz. After each click, 10 ms of the electroencephalogram was sampled and a total of 2000 responses were averaged. Two separate averages of 2000 evoked potentials were obtained and the wave latencies had to agree to within 0·1 ms before these averages were accepted.

To elicit somatosensory evoked potentials a 100 μs square wave pulse of electric current was applied over the right median nerve at the wrist, at a rate of 2 stimuli per second. The intensity of this stimulus was determined for each individual so that a twitch was induced in the muscles of the thenar eminence. To record the evoked potential over the somatosensory cortex silver/silver chloride cup electrodes (8 mm in diameter) were placed over the contralateral parietal region and centrally on the forehead,

Table *Details of subjects and changes in the evoked potentials during the study*

Subject No	*Age*	*Details of study*	*bs^1 (mmol/l)*	*bs^2 (mmol/l)*	*Whole blood ketone bodies* (mmol/l)*	*Evoked potentials*			*Clinical signs*
						Type	*Baseline (ms)*	*Change (ms)*	
					Subjects with abnormal changes				
1	1 day	S	2·4	1·4	0·03	Brainstem auditory	4·98	+0·38	None
2	1 day	S	1·9	1·4	0·01	Brainstem auditory	5·50	+0·34	None
3	2 days	S	2·1	1·9	0·40	Brainstem auditory	5·00	+0·40	None
4	2 days	F	4·1	2·5	0·05	Brainstem auditory	5·03	+0·60	Drowsy
5	3 days	S	4·2	0·7	0·05	Brainstem auditory	5·28	+0·32	None
6	0·3 years	F	3·0	2·3	0·04	Somatosensory	20·00	+4·00	Drowsy
7	1·3 years	F	3·4	2·5	5·30	Brainstem auditory	4·75	+0·56	None
8	3·9 years	F	2·6	1·6	0·40	Brainstem auditory	4·00	+0·40	Drowsy
9	15·3 years	I	3·9	0·9	ND	Brainstem auditory	4·16	+0·31	Drowsy
10	16·0 years	I	4·0	1·2	ND	Brainstem auditory	4·00	+0·32	Drowsy
					Subjects with no changes				
11	0·7 years	F	5·6		0·26	Brainstem auditory	4·75	+0·12	None
12	1·5 years	F	3·4		0·45	Somatosensory	20·00	+1·00	None
13	2·0 years	F	4·8		0·28	Somatosensory	16·60	−1·10	None
14	4·2 years	F	3·2		4·50	Brainstem auditory	4·01	+0·10	None
15	6·0 years	F	1·9		2·40	Somatosensory	14·00	+1·20	None
16	11·9 years	F	3·4		0·24	Somatosensory	17·00	0·00	None
17	12·0 years	F	3·4		0·11	Brainstem auditory	4·03	+0·14	None

bs^1=The lowest blood glucose concentration associated with normal neural function
bs^2=The blood glucose concentration immediately before the first abnormal evoked potential was recorded
*Acetoacetate and 3-hydroxybutyrate normal range when normoglycaemic is 0·02–0·49 mmol/l
ND=not done
S=Spontaneous hypoglycaemia, F=fasting, I=insulin administration

with an indifferent electrode placed over the biceps of the right arm. The impedance of the recording electrodes was maintained at 3 kohms or less. The electroencephalogram was amplified by 10^4 by a Nicolet HGA 200 Physiological Amplifier and a filter bandpass of 30–3000 Hz was used. Fifty ms of the electroencephalogram was sampled after each stimulus was applied to the median nerve and an average of 50 responses was made. Two separate averages of somatosensory evoked potentials were obtained and the latencies of the onset of the first wave (N_1) which is thought to be generated by the arrival of the afferent volley at the cortex were measured. The latencies had to agree to within 0·1 ms for the averages to be accepted.

Both brainstem auditory and somatosensory evoked potentials were plotted onto paper for immediate scrutiny and transfered to a microcomputer for later analysis.

Results

The details of the 17 subjects studied are summarised in the table.

Fig 1 shows serial recordings of somatosensory evoked potentials from a 4 month old child studied during an episode of hypoglycaemia provoked by fasting (subject 6). The base line recording of the somatosensory evoked potential shows the latency to the onset of the N_1 complex (20 ms) to be within the normal range for her age (18·9–20·1 ms) when the blood glucose concentration was 4·2 mmol/l. The latency to the onset of N_1 became prolonged (24 ms), and the wave form was less well defined, when the blood glucose concentration fell to 2·3 mmol/l. After the restoration of the blood glucose concentration to 4·1 mmol/l by an intravenous injection of 25% dextrose (2 ml/kg), the waveform became well defined and the latency returned to lie within the normal range for her age (19·5 ms).

Fig 2 shows serial brainstem evoked potentials recorded from a 2 day old baby who had recurrent 'asymptomatic' espisodes of spontaneous hypoglycaemia (subject 4). In brainstem evoked potentials the latency between the waves I and V has been shown to reflect the integrity of brain stem function[10–12] Initially the latency between waves I and V (5·03 ms) was within the normal range for a newborn infant (4·81–5·39) during normoglycaemia. The wave I–V interval remained within the normal range until the blood glucose concentration fell to 2·5 mmol/l when the I–V interval was 5·4 ms. There was a progressive prolongation of the wave I to V interval as the blood glucose concentration fell to 1·6 mmol/l when wave V could not be elicited. When the blood glucose concentration was increased to be above 4 mmol/l wave V returned but

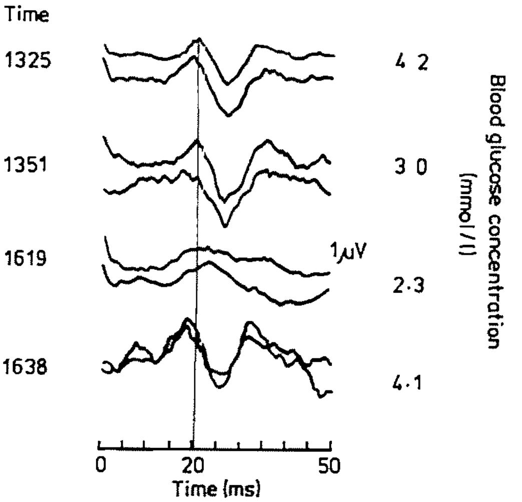

Fig 1 *Serial somatosensory evoked potentials recorded in subject 6 in relation to her blood glucose concentration. The vertical line indicates the latency of N_1 in the initial recording during normoglycaemia.*

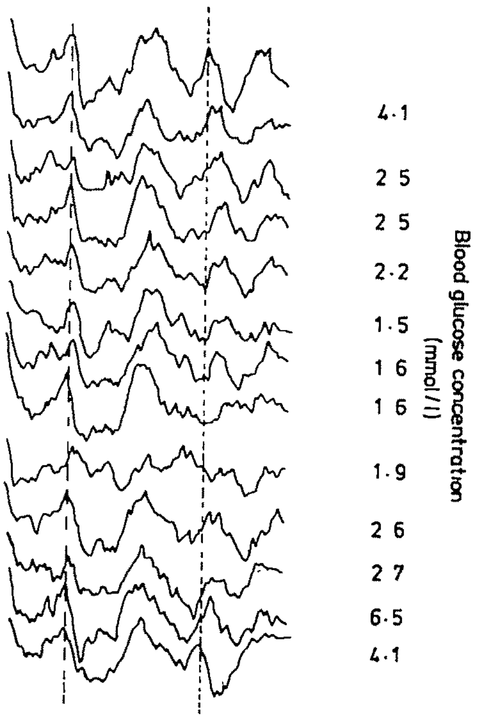

Fig 2 *Serial brainstem auditory evoked potentials recorded in subject 4 in relation to his blood glucose concentration The vertical lines indicate the latency between wave I and wave V in the initial recording during normoglycaemia*

with an abnormal wave I–V latency (5·63 ms). Despite the maintenance of a blood glucose concentration above 4 mmol/ the wave I–V interval continued to be abnormally prolonged for 16 hours (fig 3).

Abnormal changes in the evoked potentials were recorded in 10 of the 17 children studied. The data for these subjects are summarised in the table. Of these 10 children, five were 'asymptomatic' (four of whom were newborn infants) and five were 'symptomatic'; there was no significant difference ($0·05<p<0·1$, Mann-Whitney U test) in the blood glucose concentration at which the evoked potentials became abnormal between the 'symptomatic' and the 'asymptomatic' groups (fig 4).

In these 10 subjects normal evoked potentials were recorded at blood glucose concentrations ranging from 5·6–1·9 mmol/l (bs^1). The first abnormal changes in the evoked potentials were recorded in these 10 subjects in association with blood glucose concentrations ranging from 2·5 to 0·7 mmol/l (bs^2).

The evoked potentials returned immediately to normal in six children after the intravenous administration of 25% dextrose (2 ml/kg) or the intramuscular administration of glucagon (20 µg/kg). In four (subjects 1, 8, 4, and 5) the evoked potentials remained abnormal for 1 hour, 1·5 hours, 16 hours, and two days, respectively, despite the presence of normoglycaemia.

In the remaining seven subjects no changes in the evoked potentials were observed; all but one of these children maintained their blood glucose concentrations above 2·6 mmol/l throughout the study. In subject 15 normal evoked potentials were recorded at a blood glucose concentration of 1·9 mmol/l.

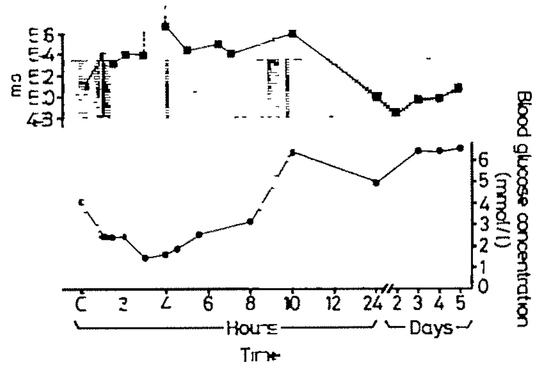

Fig 3 *The latency between waves I and V in the brainstem auditory evoked potentials recorded in subject 4 in relation to blood glucose concentration and the time from the onset of the study. The shaded area represents the normal range for the wave I–V latency (in ms) in the newborn period.*

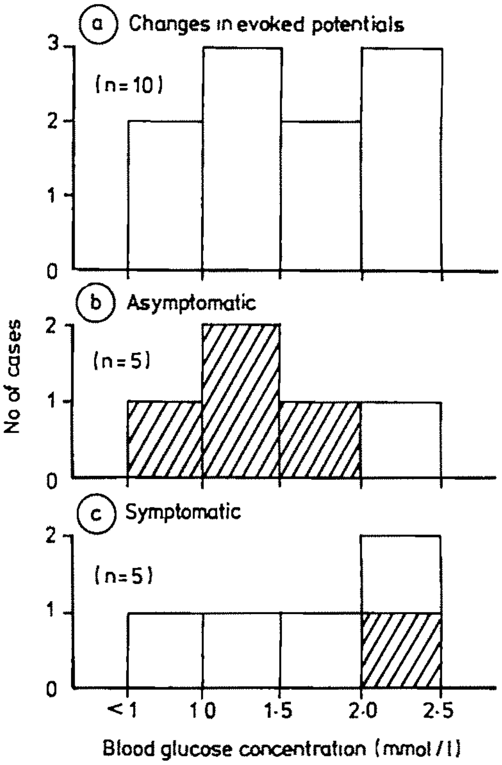

Fig 4 *(a) The blood glucose concentration that was drawn nearest to the time when the first abnormality in the evoked potentials was recorded in each subject. The subjects have been subdivided into those who were asymptomatic (b) and those who were symptomatic (c). The shaded area identifies the neonatal subjects*

Discussion

It is now nearly 30 years since Cornblath and his colleagues established hypoglycaemia to be an important cause of morbidity and mortality in the newborn infant,[1] and yet the definition and the management of hypoglycaemia continues to be a controversial and confused topic in paediatrics.[5]

Glucose has a dual role for normal brain function: as the major metabolic fuel, and as a precursor of essential macromolecules during the rapid phase of brain growth.[13] It is likely, therefore, that hypoglycaemia is particularly harmful in childhood, especially in the newborn period.

It is a common belief that 'asymptomatic' hypoglycaemia is less important than 'symptomatic' hypoglycaemia.[6] This is not supported by our findings where there was demonstrable neural dysfunction in children with blood glucose concentrations of less than 2·6 mmol/l irrespective of whether there were clinical signs. Clinical signs of disturbed neural function in the newborn baby and young child are often subtle and they may not be noted consistently even by experienced observers.[6] The data from our study suggest the division between 'symptomatic' and 'asymptomatic' hypoglycaemia is artificial and may result in treatment being delayed or witheld.

The belief that 'asymptomatic' hypoglycaemia is not harmful has arisen mainly from the findings of three follow up studies,[7 14 15] the largest of which is by Koivisto and his colleagues.[14] In their analysis of the outcome of 151 children who had had blood glucose concentrations of less than 1·1 mmol/l in the neonatal period they found that those babies with no abnormal clinical signs during the hypoglycaemia had a better outcome than those in whom abnormal clinical signs were reported. There was, however, a similar incidence of 'doubtful' outcomes in the 'asymptomatic' and 'symptomatic' groups and if the babies who had hypoglycaemic seizures were excluded from the 'symptomatic' group, there was no significant difference between the outcome of the 'symptomatic' group and the 'asymptomatic' babies. On this basis Koivisto *et al* in fact recommended 'that asymptomatic hypoglycaemia should be detected by a screening system and if it persists should be treated to avoid possible permanent central nervous system damage'.

The study by Pildes and her colleagues emphasises the need for longer term follow up of the higher mental functions of children after episodes of hypoglycaemia.[7] The results of their psychological tests suggested that as verbal skills became important in the evaluation of intellectual performance (between 5–7 years of age) a larger proportion of the hypoglycaemic children had Stanford-Binet scores below 86 in comparison with the control group. The findings by Haworth and McRae[15] and those of Koivisto's group can be criticised because both had very short follow up periods ranging from eight to 30 months.

Other investigators have studied the acute effects of hypoglycaemia on neurological function as assessed by the electroencephalogram and have shown there to be abnormalities in children during episodes of blood glucose concentrations below 2·2 mmol/l.[3] The electroencephalogram is, however, a nonspecific measure of brain function. It is difficult from these studies to determine the blood glucose concentration below which neural dysfunction occurs in neural pathways with a high rate of glucose utilisation.

The recording of evoked potentials allows objective serial measurements of neural function in specific pathways in relation to the blood glucose concentration. In this study we chose to measure the potentials evoked in neural pathways with a high rate of glucose utilisation. Studies investigating local cerebral glucose metabolism in newborn and adult primates have shown that the rate of glucose utilisation is highest in the inferior colliculus (commonly accepted as the generator of wave V in brainstem auditory evoked potentials) and that there are relatively high rates of glucose utilisation in the rest of the auditory pathway.[16] Layer IV of the cortex, the site of sensory afferent fibre input to the somatosensory areas of the cortex,[17] was also shown to have a high rate of glucose utilisation. It is reasonable, therefore, to propose that the measurement of neural activity in the somatosensory and the auditory pathways provides a sensitive index of the lowest blood glucose concentration compatible with normal neural function.

Although abnormalities in evoked potentials have been shown to be of prognostic importance in other clinical situations,[10 12] there have been no previous studies in children relating acute changes in sensory evoked potentials to the blood glucose concentration.

Our studies show that neural dysfunction occurs in children in association with low blood glucose concentrations. In two subjects (subjects 4 and 7) neural dysfunction was recorded at blood glucose concentrations as high as 2·5 mmol/l (see table; bs^2). There was intersubject variability, however, with normal evoked potentials being recorded in four subjects (subjects 1, 3, 2, and 15) in association with blood glucose concentrations of 2·4, 2·1, 1·9, and 1·9 mmol/l, respectively (see table; bs^1). It is possible that several factors contribute to this intersubject variability. First, there may be different critical concentrations of blood glucose for normal neural function in individual subjects. Second, the rate of fall of the blood glucose concentration and the duration of hypoglycaemia may determine the presence and degree of abnormal neural function. Without continuous measurements of the blood glucose concentrations it was not possible in our study to determine the relative importance of these factors. Third, it has been suggested that ketone bodies can be used for energy by the brain and may therefore have a protective effect during episodes of hypoglycaemia. Owen and his colleagues showed in adult man during starvation that alternative substrates particularly ketone bodies can be used by the brain.[18] Cerebral utilisation of ketones has been shown subsequently in children[19] and in young animals.[20]

Our data provide conflicting results concerning the protective effect of high concentrations of blood ketone bodies during hypoglycaemia. Eleven subjects had blood glucose concentrations below 2·6 mmol/l during the study; the concentration of circulating ketone bodies was measured in nine of these children. Seven children (subjects 1, 2, 3, 4, 5, 6, and 8) had hypoketonaemic hypoglycaemia and all had abnormal changes in their evoked potentials in association with low blood glucose concentrations. Two subjects (subjects 7 and 15) had hyperketonaemic hypoglycaemia. Subject 15 had normal evoked potentials with a blood glucose concentration of 1·9 mmol/l and a ketone body concentration of 2·4 mmol/l, suggestive of a protective effect from the hyperketonaemia. Subject 7, however, had abnormal evoked potentials at a blood glucose concentration of 2·5 mmol/l and with a blood ketone body concentration of 5·3 mmol/l. It may be that there is a complex interrelationship for the maintenance of normal neural function not only between blood glucose and ketone body concentrations but also between the concentration of other metabolic fuels and substrates, for example, free fatty acids, lactate, and amino acids.

It is of practical importance to note, however, that no subjects with blood glucose concentrations of 2·6 mmol/l or greater had abnormal changes in neural function. These findings are supported by the study of Harrad *et al* who found abnormalities in the visual evoked potentials of adult subjects when the blood glucose concentration was below 2·6 mmol/l.[21]

In all the 10 subjects with neural dysfunction the evoked potentials eventually returned to normal after a rise in the blood glucose concentration. In four of these subjects, however, there was prolonged neural dysfunction for up to 48 hours despite the maintenance of normoglycaemia. Although it cannot be known whether transient abnormalities in the evoked potentials are associated with permanent neural damage, such neural dysfunction cannot be beneficial and it is reasonable to try to prevent it by maintaining blood glucose concentrations at 2·6, mmol/l or above.

All our subjects were well at the time of the study. It is likely that the 'safe' blood glucose concentration may vary in different clinical situations, for example, during anoxia, polycythaemia, or convulsions. The non-invasive recording of evoked potentials provides the possibility of obtaining functional definitions of hypoglycaemia in children of different ages under a variety of clinical situations, and further studies are needed to explore these suggestions.

We would like to thank the following for their help the children and their parents, the nursing and medical staff, Dr David WA Milligan, Dr Alan Murray, and Mr Bill Hill Support from the Newcastle Health Authority is acknowledged THHG Koh is a Medical Research Council Training Fellow

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Accepted 3 May 1988

Archives of Disease in Childhood, 1988, **63,** 1359–1362

Effect of kwashiorkor on the cardiovascular system

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SUMMARY In kwashiorkor the heart is clinically and radiologically small. This study utilises echocardiography, a tool not previously used in this disease, to show that this is due to decreased muscle mass.

Malnutrition stunts growth and produces generalised tissue wasting, particularly a severe loss of muscle tissue and protein, which almost certainly includes the heart muscle. The syndrome of kwashiorkor (protein energy malnutrition) is characterised by oedema, as well as tissue loss, skin, hair, and mood abnormalities.[1] Various cardiovascular abnormalities have also been documented, including low cardiac output,[2 3] cardiac failure (reduced cardiac size),[4] and sudden unexpected death.[5]

This study was undertaken to assess both wall and chamber size as well as function of the left ventricle in children with kwashiorkor, utilising echocardiography as an entirely non-invasive and accurate tool not available to the earlier investigators cited above.

Patients and methods

All patients with the clinical features of kwashiorkor admitted to the Red Cross War Memorial Children's Hospital were screened and in the absence of severe, dehydrating diarrhoeal disease, septicaemia, or pre-existing cardiac disease were considered for the study.

Initial investigations included measuring plasma proteins and haemoglobin concentrations. Patients were only included in the study if serum albumin concentration was less than 25 g/l, confirming severe protein lack, and the haemoglobin concentration more than 70 g/l, thus excluding the cardiovascular effects of severe anaemia. Over a six month period, 21 patients aged 12 to 30 months underwent chest radiotherapy, electrocardiography, and echocardiography within 48 hours of admission.

The cardiothoracic ratio was determined from the chest radiograph (broadest diameter of the heart internal diameter of the chest). From standard 12 lead electrocardiograms the R wave amplitude in lead V6 was measured and compared with percentile charts.[6] The QT interval was also measured and corrected for rate by applying Bazett's formula (QT interval $\sqrt{\text{RR}}$ interval).[7]

Cross sectional and M mode echocardiography was performed on an Advanced Technology Laboratories Mark 300C machine. The M mode recordings were checked by two observers, and all measurements were made according to the American Society of Echocardiography standards.[8] Direct measurement was made of the left ventricular dimension at end systole (LVES) and end diastole (LVED), and left ventricular wall thickness from the widths of the interventricular septum and the posterior left ventricular wall. These values were compared with percentile charts,[9] and derived values for left ventricular function were obtained from the formula:

$$\text{shortening fraction} = \frac{\text{LVED} - \text{LVES}}{\text{LVED}} \text{ respectively}$$

Results

All 21 patients had chest radiography. The cardiothoracic ratio was below 60% in all. Twenty out of 21 (95%) had ratios less than 55%; 14 of the 21 had values less than 49%. Nineteen patients had electrocardiography; the QTc was normal in all. The amplitude of the R wave in V6 was less than the 25th centile (as compared with age related centiles) in 18 (95%) of patients,[6] and less than the 5th centile in seven (37%). Twenty of the 21 patients had values within the 95% predictive values for the left ventricular end diastolic dimension for body surface area (fig 1). Eighteen of the 21 patients were within the predictive values for the end systolic dimension (fig 2). Overall 19 (90%) had values above the 5th centile for body surface area.

As regards the ventricular wall measurements 17 (81%) patients had values below the 5th centile for

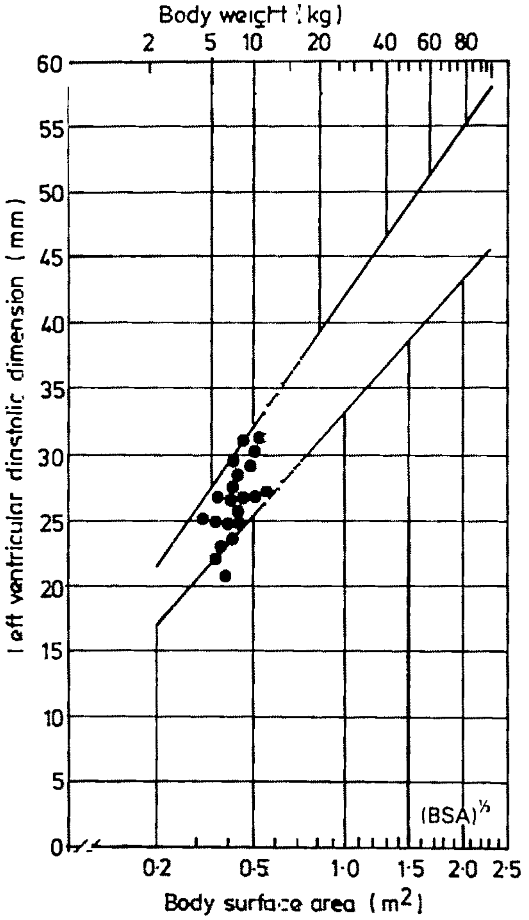

Fig 1 *Left ventricular diastolic dimension according to body surface area with the 95% prediction intervals drawn for assessment.*[9]

the interventricular septal measurement (fig 3) and 15 (71%) for the posterior wall (fig 4). Overall 16 (76%) had values equal to or below the 5th centile for one or both variables. Twenty patients had normal contractility as measured by the shortening fraction—that is, a value of 30% (mean=38%). One patient had a shortening fraction of 25%.

Discussion

This study has shed new light on some unanswered questions on the cardiovascular consequences of kwashiorkor. The presence of a small heart, in the *early* stages of the illness has been confirmed, and the cause of this lies in decreased myocardial tissue. The septal thickness or left ventricular posterior wall thickness or both were below 5th centile lines in 74% of patients, whereas the left ventricular chamber dimensions were above the 5th centile lines in 90%. This is in accord with postmortem studies showing very low cardiac mass.[5] Left ventricular function is initially well preserved despite the loss of myocardial tissue, and the shortening fraction was above 0·30 in all but one patient. At presentation, impaired contractility is thus not a cause of low cardiac output, and the results obtained from dye dilution studies[3] may have been confounded by other variables—for example, leakage of dye out of the intravascular compartment and excessive dilution of dye due to anaemia in the early stages.

Decreased muscle mass at initial presentation may be the cause of later cardiomegaly and cardiac

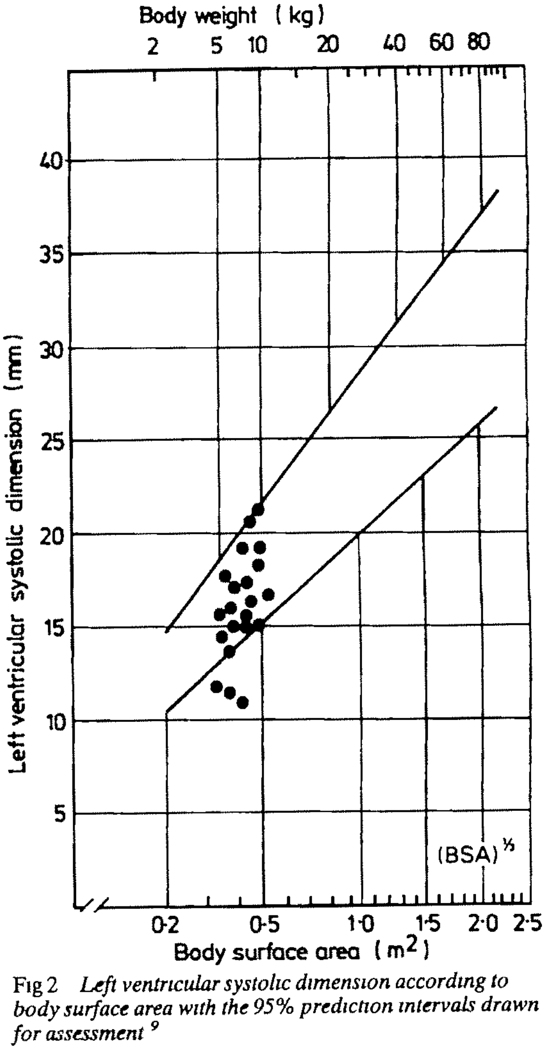

Fig 2 *Left ventricular systolic dimension according to body surface area with the 95% prediction intervals drawn for assessment*[9]

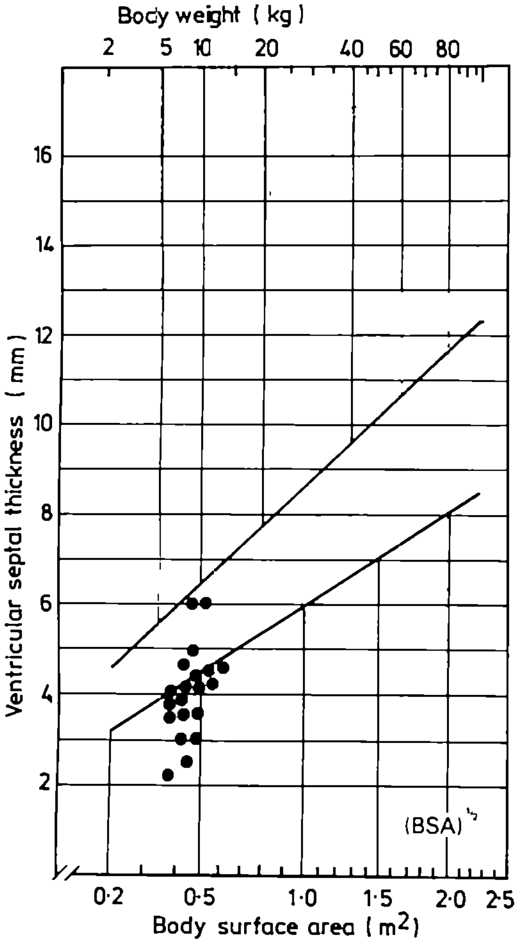

Fig 3 *Ventricular septal thickness according to body surface area with the 95% prediction intervals drawn for assessment.*[9]

failure in the refeeding stage,[10] as the left ventricle may not be able to respond to increases in left ventricular preload, especially with inappropriate salt loading.[4]

Sudden cardiac death also occurs during refeeding and some histological studies have shown structural breakdown of myocardial elements during starvation.[11 12] Arrhythmias have been implicated as a cause for sudden death during refeeding. Prolongation of the QT interval was well documented by Smythe *et al*,[5] but they could not show this consistently in their patients who subsequently died. More recent studies in fasting adults have confirmed this observation, and further implicated QT prolongation as a factor in sudden death.[13] No abnormal QT intervals were recorded in this study, but all electrocardiograms were obtained on admission and not during the refeeding stage.

A recent study that compared subjects with kwashiorkor with age matched controls confirms our findings of reduced myocardial mass with preserved left ventricular function.[14] We have used standard centile curves, and although there may be racial differences in cardiac dimension (all our patients were black) these are very small in the age range 12 to 30 months.[15]

The treatment of kwashiorkor should therefore be directed at gradual correction of fluid, electrolyte, and nutritional disturbance, and early treatment of secondary infections as it appears that although primary myocardial dysfunction is not present, there is a decreased myocardial mass, which may lead to

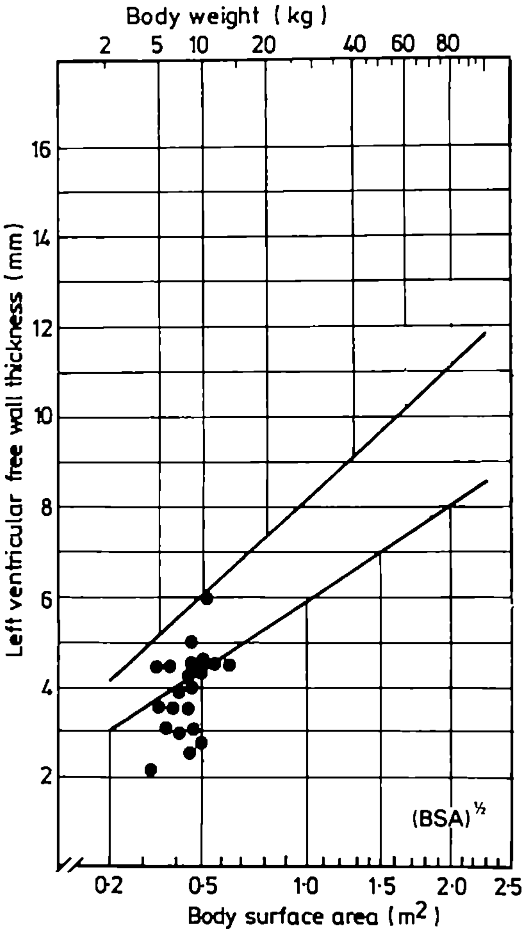

Fig 4 *Left ventricular free wall thickness according to body surface area with the 95% prediction intervals drawn for assessment.*[9]

an inability of the ventricles to respond to increases in ventricular preload.

Further echocardiographic studies during refeeding are required to show the left ventricular response to an increased preload in children with kwashiorkor.

We thank Miss K Leahy for secretarial help with the manuscript and the medical superintendent of the Red Cross War Memorial Children's Hospital, Dr RO Simpson, for permission to publish

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Accepted 22 March 1988

Archives of Disease in Childhood, 1988, **63,** 1363–1367

Late onset ornithine carbamoyl transferase deficiency in males

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SUMMARY Six boys with ornithine carbamoyl transferase deficiency presenting in infancy or later childhood are described. There was wide variation in both the time of presentation and the symptoms, which may initially suggest a neurological, behavioural, or gastroenterological problem. Two patients died, as did two male siblings who were probably affected, but with early recognition of the hyperammonaemia the outlook is good.

Primary deficiency of ornithine carbamoyl transferase (EC 2.1.3.3) is the most common of the inherited disorders of the urea cycle. It has an X linked mode of inheritance and the hemizygous male usually develops severe hyperammonaemia in the neonatal period. The illness progresses rapidly with convulsions, coma, apnoea, and almost invariably death unless treated intensively.[1]

Although most of the affected males present in the neonatal period, a number have been reported who have presented later in infancy,[1] during childhood, or even in adult life. In some of these male patients the enzyme activity was reduced, which may explain the late onset,[2 3] while in others the deficiency appeared to be complete despite the late presentation.[4 5]

In this paper we describe six male patients with ornithine carbamoyl transferase deficiency who presented after the neonatal period. There was wide variation in the age of presentation and the symptoms. Certain aspects of two of the patients (cases 4 and 5) have been reported previously.[6]

Methods

Enzyme activity was measured in biopsy specimens—liver or jejunal mucosa—by the method of Nuzum and Snodgrass with modifications,[7] and urinary orotic acid by the method of Harris and Oberholzer.[8]

Case reports

The salient clinical features are summarised in table 1.

CASE 1

This boy was born by caesarean section for fetal distress and weighed 3800 g. During childhood his parents complained that he was a very difficult child, introverted with 'volcanic' tempers. At the age of 12 years he had an episode of confusion for which he was admitted to hospital, but no cause was found. Drug or solvent abuse was suspected. Subsequently he had three further episodes and during one of these he was noted to have a raised ammonia concentration. A protein load was clearly abnormal, but nothing further was done. At the age of 14 years he was admitted to hospital deeply unconscious. Four days before admission the patient had complained of feeling sleepy and the next day he was upset, demanding, and difficult. He then became confused and uncoordinated. The night before admission he had a high protein meal and the next morning he was found to be unrousable and limp. On admission he was unconscious with a paraparesis. The plasma ammonia concentration was 292 μmol/l. He was treated with intravenous sodium benzoate with a rapid fall in plasma ammonia (figure), however, he did not recover consciousness for three days. Urine orotic acid excretion was raised and his mother was found to be a carrier (table 2). Since then he has been treated with a low protein diet, arginine supplements, and sodium benzoate. He has remained generally well, although he has had further episodes of hyperammonaemia, particularly precipitated by energy restriction. At the age of 18 years he passed three 'A' levels at A grade and was accepted at medical school.

Table 1 *Summary of clinical features of late onset ornithine carbamoyl transferase deficiency*

Case No	Symptoms before diagnosis	At diagnosis		Outcome
		Age	Symptoms and signs	
1	From 12 years: episodes of confusion (?volcanic tempers')	14 years	Lethargy and confusion progressing to coma and paraparesis	Alive
2	At 17 months. one episode of vomiting and drowsiness, ataxia, 'visual problems' (see text)	24 months	Vomiting, drowsiness	Alive
3	Investigated prospectively because of brother (case 2)			Alive
4	Vomiting and drowsiness with infections recent school progress poor	12 years	Vomiting, confused, 'could not see' progressing to variable conscious level	Dead
5	From 8 months irritability, vomiting	12 months	Vomiting, coma	Dead
6	At 10 months: irritability, vomiting	11 months	Irritability, vomiting, and myoclonic jerks	Alive

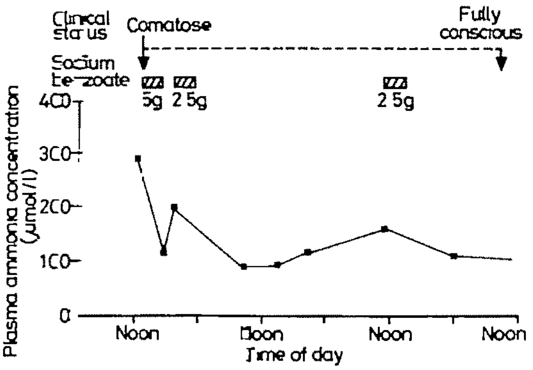

Figure *The course of plasma ammonia concentrations during an episode of encephalopathy treated with intravenous sodium benzoate in case 1.*

CASES 2 AND 3

Cases 2 and 3 are from the same family of four boys.

The first child in the family was born after a normal pregnancy and delivery. He was well until 16 months of age when he died after a short encephalopathic illness labelled as a 'cerebral degeneration'.

The second in the family (case 2) became ill for the first time at the age of 17 months when he was admitted to the hospital after two days of vomiting, drowsiness, ataxia, and visual problems (inability to focus on objects, dilatation of pupils, with little reaction to light or dark). He was treated with intravenous fluids and was back to normal within a week. At the age of 24 months he started intermittent vomiting every four to five days. During one episode he became drowsy and floppy. The plasma ammonia concentration was 330 µmol/l, with abnormal liver function, and raised urine orotic acid concentration. Ornithine carbamoyl transferase deficiency was confirmed by enzyme studies (table 2).

Table 2 *Biochemical features of late onset ornithine carbamoyl transferase deficiency*

Case No.	Initial plasma ammonia concentration (µmol/l)	Orotic acid: creatinine ratio (µmol mmol)*	Enzyme activity		Mother's carrier status	
			Ornithine carbamoyl transferase†	Carbamoyl phosphate synthetase‡ (µmol/g/hour)	Family history	Loading test
1	104	630	Not done	–	–	+
2	330	51	110	72	+	Not done
3	62	2·6	1 8 (jejunal mucosa)			
4	286	695	209	271	–	Refused
5	700	462	233	—	+	+
6	214	2800	372	195	–	+

Reference ranges—*orotic acid:creatinine ratio (µmol mmol) at 2 weeks—10 years, 0 5–3·3 and >10 years, 0·4–1·2; †ornithine carbamoyl transferase activity, 2200–10 700 µmol/g/hour, and ‡carbamoyl phosphate synthetase activity, 76–515 µmol/g/hour.

He was treated with a low protein diet and he remained well up to the age of 6½ years when he developed abdominal pain and vomiting. He became drowsy, ataxic, and confused but he recovered after treatment with intravenous fluids and sodium benzoate. Although he does not keep consistently to the diet, he is now 9 years old, growing normally, and attends a normal school.

The other boy (case 3) is the fourth in the family. He was born after a normal pregnancy weighing 3600 g, and he had no perinatal problems. At the age of 1 month he was investigated for ornithine carbamoyl transferase deficiency because of his brother's history Although the plasma amino acids and orotic:creatinine ratio were normal, plasma ammonia concentration was slightly raised and the ornithine carbamoyl transferase activity in jejunal mucosa was low (1·8 μmol citrulline/mg protein/hour (normal more that 51). He was well until the age of 13 months, when he developed bronchiolitis and became semicomatose. The ammonia concentrations rose to 147 μmol/l. He recovered quickly with intravenous fluids. He has had no further problems and is developing normally.

CASE 4 (case 5 in reference 6)
This boy, the only child in the family, was born by caesarean section after a failed trial of labour at 37 weeks' gestation; he weighed 2500 g. There were no neonatal problems. All his life he tended to vomit, particularly with infections, and occasionally he had been very drowsy during the episodes of vomiting but he always recovered spontaneously.

He became seriously ill for the first time at the age of 12 years when he was admitted with a two day history of vomiting, irritability, and deterioration of conscious level. He had not been doing well at school, however, and had recently been removed from his present school by his parents. For three days before his admission he had been vomiting but the parents were not particularly worried because of his history. On the third night he woke up from bed confused, incoherent, and said he could not see. He was admitted to a private nursing home and sedated with chlorpromazine, but then became more restless. He was admitted to the Hospital for Sick Children because of deteriorating conscious level. On examination he was drowsy and confused but rousable, screaming from time to time. He had no focal neurological signs. The plasma ammonium concentration was 236 μmol/l and the plasma glutamine and alanine were also raised. He was treated with intravenous fluids and later peritoneal dialysis. The plasma ammonia concentrations initially fell to 186 μmol/l, but 24 hours after admission he had a fit and his condition deteriorated rapidly. His ammonia rose to more that 2000 μmol/l and he died. Enzyme studies on a liver biopsy specimen were performed immediately after death and confirmed ornithine carbamoyl transferase deficiency (table 2). The family have refused further investigation.

CASE 5 (case 7 in reference 6)
This boy was born spontaneously but prematurely at 28 weeks' gestation; he weighed 1090 g A brother had died of an encephalopathic illness aged 3 months. The patient was well until the age of 3 days when he started having apnoeic attacks. At the age of 24 days he developed Klebsiella pneumonia and meningitis with convulsions and soon after that necrotising enterocolitis. With intravenous feeding he recovered and was developing normally until the age of 8 months, when he became irritable and started vomiting. At the age of 12 months he was readmitted to hospital unconscious after severe vomiting. His condition deteriorated rapidly and he died. The plasma ammonia concentration was 700 μmol/l and the ornithine carbamoyl transferase activity of a specimen from needle biopsy taken immediately after death was reduced (table 2).

CASE 6
This boy was born after a normal pregnancy and delivery; he weighed 3200 g. There were no neonatal problems, but he did not feed well. He became ill for the first time at the age of 10 months when he was admitted to hospital with persistent vomiting and irritability. On examination there were no specific clinical signs. The only abnormal biochemical investigation was a slight rise in plasma aminotransferase activities. The ammonia concentration was not measured. Minor immunological abnormalities were detected and a diagnosis of food allergy made. One month after being admitted to the hospital he again became ill with episodes of lethargy, vomiting, irritability, and myoclonic jerks. His plasma ammonia concentration was raised (214 μmol/l) with abnormal liver function. Urine orotic acid after a protein load was raised suggesting ornithine carbamoyl transferase deficiency, which was confirmed by enzyme studies (table 2). A computed tomogram showed cerebral oedema. He was treated with a low protein diet, and has since done well on a normal diet with sodium benzoate.

Discussion

Ornithine carbamoyl transferase deficiency is X linked and most of the males are born with no detectable residual enzyme activity. They develop a severe illness in the neonatal period and unless intensively treated will die in the early months of life. Females have a much more variable presentation ranging from severe disease in infancy to those who remain asymptomatic. Males with mild disease have generally been considered to be rare and in a recent review only 18 cases were documented.[1] Ten further males have been described since then,[9–15] and a number of others are incompletely reported. Most of the patients have presented in infancy with anorexia, vomiting, irritability, failure to thrive, and episodic encephalography. However, some patients have not presented until adult life.[16 17] Sixteen out of the 28 patients died. We have described a further six patients with symptoms presenting as late as 12 years of age and it is likely that two other boys in these families, both of whom died, were also affected (siblings of cases 2 and 3 and 5).

The initial symptoms of hyperammonaemia are varied and may be subtle, including confusion, irritability, or behavioural problems. These may be misdiagnosed as psychiatric problems, drug abuse, and food allergy. Two patients complained of visual disturbances. Alternatively, the main symptom may be vomiting, particularly at times of metabolic stress such as infections so that a gastrointestinal disorder may be suspected. This presentation is common in infancy, combined with poor developmental progress. Routine biochemical investigation often shows raised plasma aminotransferase activities suggesting 'hepatitis'.

The mainstay of day to day treatment is a low protein diet, although patients with late onset ornithine carbamoyl transferase deficiency may need only modest protein restriction (1·5–2·2 g/kg/day). Some will even be able to tolerate a normal diet. Other patients may prefer to eat a normal diet and to take sodium benzoate rather than be confined in what they eat. This compound is used to form an alternative pathway to urea for nitrogen excretion.[18] It is conjugated in the liver with glycine to form hippuric acid, which is rapidly excreted in the urine, thereby removing excess nitrogen. Given orally it is an effective and well tolerated drug for reducing plasma ammonia concentrations. The dose should not routinely exceed 250 mg/kg per day without monitoring plasma concentrations.[19]

Arginine is normally synthesised within the urea cycle and is not an essential amino acid. In ornithine carbamoyl transferase deficiency, however, because of the metabolic block it may become essential or semiessential in the more severely affected patients. Some with the late onset forms of ornithine carbamoyl transferase deficiency may require additional arginine supplements during periods of rapid growth or when the plasma arginine concentrations are very low (less than 30 μmol/l).[19]

Although the patients with late onset ornithine carbamoyl transferase deficiency may remain well for long periods, there is always a risk that hyperammonaemia may progress to more serious neurological problems such as coma and focal signs such as paraplegia and hemiplegia. Computed tomography may show focal hypodense areas.[6] Once a child has reached this stage, unless the diagnosis is made rapidly and the correct treatment instituted, the outlook is poor. Nevertheless, with early and effective treatment with sodium benzoate, as in case 1, the outlook can be excellent. The usual dose in these circumstances is 250 mg/kg given over four hours and followed by the same dose in the next 20 hours.[19]

The factors that precipitate an attack are not always understood and there may be long intervals between hyperammonaemic episodes. Although infection is a common precipitating factor, not all infections cause problems, the response being unpredictable. It is particularly difficult to explain why the boy in case 5 did not develop severe hyperammonaemia in the neonatal period when he had a severe infection. Energy restriction was a contributing factor in the episodes of hyperammonaemia of case 1 accelerating protein catabolism and hence hyperammonaemia.

We would like to thank Drs J Wilson and M J Dillon for permission to publish the case reports of the children who were under their care. Mr A Whitfield and Professor A D Patrick for the enzyme analyses, and Mr V G Oberholzer for the measurement of orotic acid.

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Accepted 2 June 1988

September 1988 we have diagnosed an additional case in a boy aged 6 months who had repeated episodes of screaming, irritability, and drowsiness lasting several days

Archives of Disease in Childhood, 1988, **63,** 1368–1371

Serum thyroxine and thyroid stimulating hormone concentrations after treatment of congenital hypothyroidism

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SUMMARY Serum thyroid stimulating hormone and thyroxine concentrations were monitored in 42 infants who had been treated for congenital hypothyroidism. Serum thyroid stimulating hormone concentrations were raised in 22 of the infants (52%) at 2 to 4 months, in 16 (38%) at 5 to 11 months, in 14 (33%) at 12 to 18 months, and in eight (19%) at 2 to 4 years. Serum thyroxine and the dose of L-thyroxine/kg/body weight were significantly lower in those infants with raised thyroid stimulating hormone concentrations. Thyroid stimulating hormone was appropriately suppressed when the dose of L-thyroxine was increased, and only one child had delayed maturation of the hypothalamic/pituitary/thyroid axis. We believe it is the infant's rapid gain in weight in the first two years of life that necessitates this decrease in the dose of L-thyroxine/kg body weight and recommend that the treatment of this age group is reviewed every two to three months.

Screening programmes for congenital hypothyroidism were first reported in 1975[1 2] and are now practised in many countries. Initial reports confirmed their efficacy and detailed the children's normal growth and development,[3–5] though recent studies have suggested that these children may not perform as well as normal controls.[6–8] This may reflect inadequate treatment and it is unfortunate that there are few reports[9–11] and only one longitudinal study[12] that have examined the serum thyroxine concentrations after treatment.

We now report plasma thyroid stimulating hormone and thyroxine concentrations after replacement treatment in children detected in the congenital hypothyroid screening programme in the South West region of England between 1981 and 1986. We have correlated these concentrations with the dose of L-thyroxine/kg body weight in an attempt to calculate optimal dosage regimens.

Patients and methods

The infants screened were those born in the South West region of England from 1981 to 1986. Capillary blood samples for the measurement of thyroid stimulating hormone were collected in duplicate on filter paper when babies were 7 days old and sent to the regional screening laboratory at Southmead Hospital, Bristol. Thyroid stimulating hormone was measured by an immunoradiometric assay (sensitivity 8 mU/l, interassay variation 12%). A blood spot thyroid stimulating hormone concentration of <25 mU/l was regarded as normal; a concentration of >80 mU/l was considered abnormal and infants were referred to a local paediatrician for clinical assessment and further biochemical investigations. Repeat blood spots were requested on neonates whose blood spot thyroid stimulating hormone concentrations were in the range 25 to 80 mU/l. If the blood spot thyroid stimulating hormone was >25 mU/l on repeat analysis the infant was referred to a local paediatrician for further investigations. The Medical Research Council definition of congenital hypothyroidism was adopted. This comprises a plasma or serum total thyroxine concentration by quantitative analysis of less than 65 nmol/l, or a plasma or serum thyroid stimulating hormone concentration by quantitative analysis of more than 10 mU/l.

Treatment with L-thyroxine and the children's progress were supervised by the local paediatricians. Treatment was monitored by the filter paper capillary blood assay for thyroid stimulating hormone. If the blood spot thyroid stimulating hormone concentrations were higher than the detection limit of the assay (8 mU/l), paediatricians were advised to check the plasma or serum concentrations of thyroxine and thyroid stimulating hormone

We identified through the screening laboratory all children with raised serum or plasma thyroid stimulating hormone concentrations (that is, >10 mU/l) and extracted clinical and biochemical data and treatment regimens from their hospital case notes. The data were analysed by comparing those with raised plasma thyroid stimulating hormone concentrations with those with normal concentrations. Comparison of the serum thyroxine concentrations and doses of L-thyroxine between the two groups was by the Mann-Whitney test and Student's *t* test, respectively. Statistical analysis was done of the pooled results and of the results at different ages.

Results

The population of the south west of England is roughly three million, and the annual birth rate about 37 000, and 185 723 infants (99% of all newborn babies) were screened between 1981 and 1986. The recall rate for a repeat sample was 0·11%.

Forty two infants (16 boys and 26 girls) had primary congenital hypothyroidism according to the Medical Research Council definition. The incidence is 1:4400. Seven other infants (five boys, two girls) had raised plasma thyroid stimulating hormone concentrations and total thyroxine concentrations within the normal range (all were more than 100 nmol/l). Three have subsequently become hypothyroid (unpublished observations).

The mean age at diagnosis was 13·8 days (range 9–18), that at starting treatment was 16 days (range 9–38), and that at the time of study was 31·5 months (range 6–63).

After treatment the serum thyroid stimulating hormone concentrations were raised in 22 of the infants (52%) between 2 and 4 months, in 16 (38%) between 5 and 11 months, in 14 (33%) between 12 and 18 months, and in eight (19%) between 2 and 4 years. Serum thyroxine concentrations were never below the normal range for age throughout the study period but were significantly lower in the infants with raised thyroid stimulating hormone concentrations ($p <0\cdot0001$) (fig 1 and table). Only one infant had persistently raised thyroid stimulating hormone concentrations in the presence of serum thyroxine concentrations in the upper part of the normal range and a satisfactory thyroxine dose/kg body weight (described as 'delayed maturation' in the figures). In all other instances thyroid

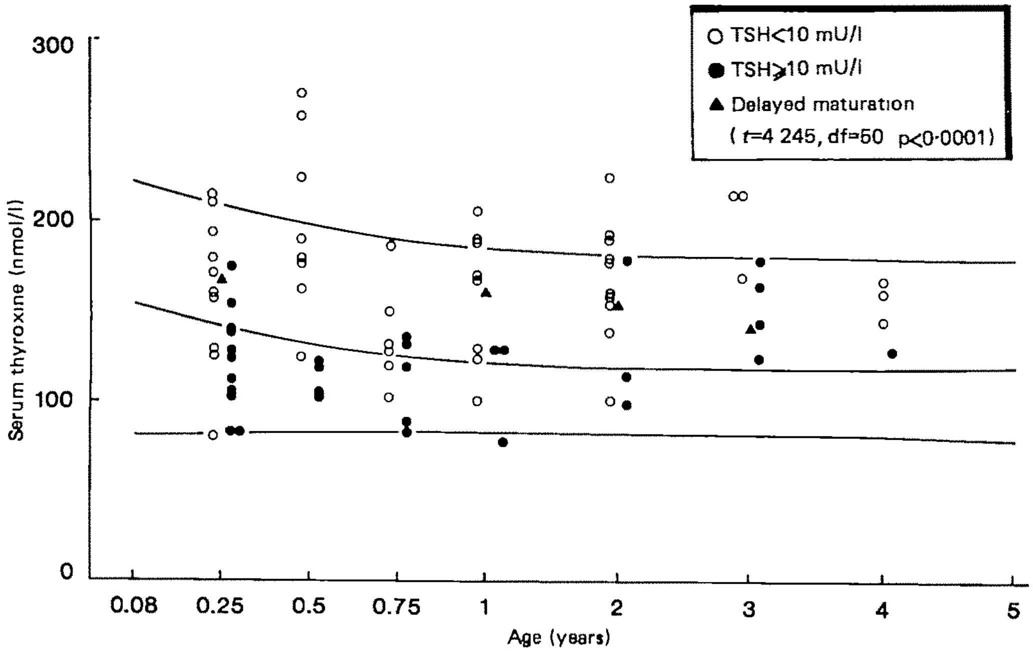

Fig 1 *Serum thyroxine concentrations in children with normal or raised thyroid stimulating hormone.*

Table *Mean serum thyroxine concentrations (nmol/l) in children with normal or raised thyroid stimulating hormone (TSH) concentrations during the study*

Age (years)	*Mean TSH concentration (mU/l)*	
	<10	*≥10*
0·25	165	120
0·5	198	111
0·75	148	111
1	160	113
2	166	122
3	199	152
4	159	128

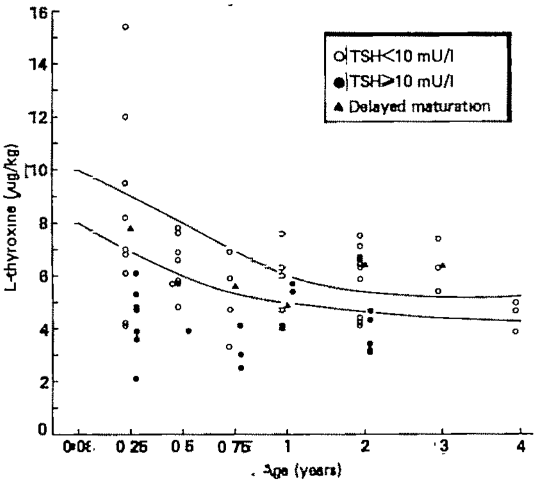

Fig 2 *L-thyroxine dosage (µg/kg/body weight) in children with normal or raised serum thyroid stimulating hormone concentrations.*

stimulating hormone was normally reduced when the dose of L-thyroxine was appropriately increased

The dose of L-thyroxine/kg body weight varied widely at all ages throughout the study period but this was most pronounced in early infancy. The mean L-thyroxine doses/kg body weight were significantly lower in infants with raised thyroid stimulating hormone concentrations (p<0·0001) (fig 2).

The growth and development of all the children were recorded as normal.

Discussion

Our results confirm those of earlier studies that showed that serum thyroid stimulating hormone concentrations remain raised in a number of children who have been treated for congenital hypothyroidism.[9] [10] [11] [12]

The only study comparable with our own[12] reported that one third of 36 infants treated for congenital hypothyroidism had raised serum thyroid stimulating hormone concentrations at 1 year of age. The authors observed that those children with raised thyroid stimulating hormone concentrations had lower serum thyroxine concentrations and had received lower doses of L-thyroxine/kg body weight. They suggested that the raised thyroid stimulating hormone concentrations was due either to an alteration in the set point of reduction, or to under treatment.

Other reports are less comprehensive. Sato *et al*[9] studied nine children with athyrotic or ectopic hypothyroidism diagnosed between 6 months and 17 years of age. They defined euthyroidism as a basal thyroid stimulating hormone concentration of <10 mU/l and a normal thyroid stimulating hormone response to thyrotrophin releasing hormone, and concluded that the pituitary threshold for regulation of thyroid stimulating hormone release by thyroxine is higher in infants and young children, and gradually decreases over several years. They recommended that the dose of L-thyroxine/kg body weight should be comparatively higher in infancy and decrease through childhood.

Schultz *et al*[10] reported five infants with congenital hypothyroidism and persistently raised thyroid stimulating hormone concentrations up to 24 months of age. The dose of L-thyroxine was appropriate, though in the lower half of the recommended range for age in four of the infants, and inadequate in the fifth. Serum thyroxine was measured on 34 occasions and all but one were within the lower range of normal. Thyroid stimulating hormone was normally reduced in four infants when their serum thyroxine concentrations rose into the upper range of normal. Schultz *et al* suggested that the hypothalamic/pituitary threshold for reduction of thyroid stimulating hormone is unusually high in infancy and their data confirm the need for serum thyroxine to be kept in the upper range of normal.

Our results show that although serum thyroxine concentrations were within the normal range for age for all the children, there was a negative correlation between their serum thyroid stimulating hormone and thyroxine concentrations and their serum thyroid stimulating hormone and thyroxine dose when expressed by kilogram body weight. Individually, when their thyroxine doses were increased their serum thyroid stimulating hormone concentrations were normally reduced. We believe that it is the infants' rapid increase in body weight that provokes this decrease in the prescribed dose of L-thyroxine/kg body weight so that serum thyroxine concentrations fall and thyroid stimulating hormone concentrations rise.

A number of reports have confirmed that the dose of thyroxine/kg body weight is high in infancy and decreases through childhood into adult life.[13 14 15] These recommended doses range from 8–10 μg/kg in infancy to 5–6 μg/kg in early childhood, and fall to 3–4 μg/kg in later childhood. Our data confirm these doses.

Some authors believe that delayed maturation of the hypothalamic/pituitary/thyroid axis is the reason for the persistently raised thyroid stimulating hormone concentrations in early childhood in children treated for congenital hypothyroidism. We believe that this is rare, and the term should be limited to those infants in whom appropriate doses of L-thyroxine are given, in whom serum thyroxine is persistently in the upper range of normal, and in whom the thyroid stimulating hormone remains raised. Only one infant in our study fulfilled these criteria.

Our data confirm that a raised thyroid stimulating hormone concentration after treatment for congenital hypothyroidism generally denotes undertreatment. A similar conclusion was reached by Frost and Parkin in a study in older children, 22% of whom had raised thyroid stimulating hormone concentrations and were receiving inappropriate treatment.[16]

There is some evidence that infants apparently being adequately treated for congenital hypothyroidism do not perform as well as controls.[5–8] Whether this is due to events before or after birth is unknown, but it does reinforce the need for careful surveillance of the children's treatment. We recommend that the infants are reviewed every two months during the first year of life when body weight is increasing rapidly. Then if the serum thyroid stimulating hormone is raised the serum thyroxine must be checked and the dose of L-thyroxine increased to maintain it in the upper range of normal. If this is done it will prevent undertreatment and the inappropriate diagnosis of delayed maturation of the hypothalamic/pituitary/thyroid axis.

We thank the paediatricians in the South West region for their help

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Accepted 14 June 1988

Archives of Disease in Childhood, 1988, **63,** 1372–1376

Treatment of renal failure in neonates

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SUMMARY Thirty neonates with acute renal failure were studied, 27 of whom died (90%) including nine of 12 treated by peritoneal dialysis. Three main aetiological groups were identified. Septicaemia was a principal cause of late onset acute renal failure, with an incidence equal to that of serious perinatal disorders. It is recommended that tolazoline should be used with caution in the treatment of hyperkalaemia as it may have a role in the aetiology of acute renal failure, the incidence of which is increasing.

The incidence of acute renal failure is increasing among neonates. This is partly because of increased awareness of the possibility of renal failure,[1–3] partly because clinicians are better at prolonging survival [4] and partly from the use of drugs that may have a profound effect on renal function and perfusion. Tolazoline, which is used in the treatment of pulmonary hypertension,[5 6] also has an effect on peripheral vascular resistance causing systemic hypotension. It has already been implicated as cause of acute renal failure in neonates.[7] The use of indomethacin for the closure of a patent ductus arteriosus may be associated with a fall in urine output and a rise in serum urea concentration.[8 9]

Since 1981 acute renal failure among newborn babies has become more common at this hospital; we therefore describe and analyse our experience of a group of 30 patients.

Patients and methods

The study group comprised those babies born between the beginning of 1981 and the end of June 1985 who at some stage during life were diagnosed as having been in acute renal failure, although this had not necessarily contributed directly to their deaths and may have resolved before death. Babies treated by peritoneal dialysis who survived were also included. Data were abstracted retrospectively from the hospital records

Acute renal failure was defined as anuria (no urine voided for at least 24 hours), or documented concern by the clinician about poor urine output over a 24 hour period together with either a serum urea concentration of more than 10·0 mmol/l (normal ranges 1·5–6·7 mmol/l for premature babies, and 1·6–4·6 mmol/l for babies born at full term)[10] or a serum potassium concentration of more than 7·5 mmol/l (normal ranges 4·5–7·2 mmol/l for premature babies, and 3·6–5·7 mmol/l for babies born at full term).[10]

The onset of renal failure was the day on which poor urine output was first noted or the serum urea concentration first exceeded 10 mmol/l.

Results

Thirty babies were studied; 27 died, and three of the 12 who had been treated by peritoneal dialysis survived. The mean (SD) gestational age of the study group was 30·9 (4·5) weeks and the mean (SD) birth weight 1610 (800) g. Twenty five (83%) were born prematurely, nine at less than 28 weeks' gestation.

In 1981 three babies were recognised as fitting the study criteria, in 1982 there were five; in 1983, six; in 1984, 11; and in the first six months of 1985, there were four. One further baby was included from 1984 whose serum urea concentration rose to 25·1 mmol/l over three days. Although poor urine output was not documented, she received three doses of intravenous frusemide for increasing oedema. Seventeen babies (57%) were anuric.

Analysis showed that the babies could be divided into four aetiological groups: perinatal haemorrhage or asphyxia or both; septicaemia; surgical problems complicated by right to left vascular shunts; and miscellaneous (tables 1 and 2).

The mean age at onset of renal failure was 7·8 days, but if those whose renal failure was due to septicaemia were excluded this fell to only three days.

Peritoneal dialysis was used for a mean of two days, the longest period being six days in a baby who

Table 1 *Numbers of babies each year in each aetiological group*

Year	*Haemorrhage or asphyxia*	*Septicaemia*	*Surgical problems*	*Miscellaneous*	*Total*
1981	0	0	2	1	3
1982	2	1	1	1	5
1983	2	3	1	0	6
1984	6	5	0	1	12
1985	0	0	1	3	4
Total	10	9	5	6	30

Table 2 *Details of the main aetiological groups*

Diagnosis	*No of babies*	*Mean (SD) gestation (weeks)*	*Mean (SD) birth weight (g)*	*Median (range) age at onset of renal failure (days)*	*Median (range) age at death (days)*	*Mean (SD) peak urea concentration (mmol/l)*	*Mean (SD) peak potassium concentration (mmol/l)*
Haemorrhage or asphyxia, or both	10	29·1 (2·0)	1360 (430)	2 (1–3)	3·5 (2–11)	17·6 (6·8)	9·0 (2·2)
Septicaemia	9	28·2 (3·6)	1090 (570)	14 (3–57)	15 (4–60)	11·7 (6·0)	8·8 (2·3)
Surgical problems with right to left shunt	5	38·6 (0·5)	2860 (370)	2 (2–4)	6·5 (3–23)	14·7 (6·1)	6·0 (2·0)
Miscellaneous	6	31·3 (3·1)	1790 (740)	3 (2–8)	5 (2–18)	27·6 (14·6)	7·3 (1·9)

had renal cystic dysplasia. All three survivors were dialysed for two days.

DIAGNOSES

Haemorrhage or asphyxia or both (n=10)—Asphyxia, defined as an Apgar score of 5 or less at 5 minutes of age, occurred in six babies. Four babies were born after abruptio placentae and another four had severe internal haemorrhages resulting in falls in their haemoglobin concentrations of more than 30%. No patient in this group survived and none was offered peritoneal dialysis.

Septicaemia (n=9)—In eight babies organisms were grown from blood after culture in two different culture media, and one baby was diagnosed as having septicaemia because of his clinical appearance in association with a gut perforation caused by necrotising enterocolitis. No patient in this group survived, although four were treated with peritoneal dialysis.

Surgical problems (n=5)—The clinical courses of these babies were complicated by right to left vascular shunting. Four had diaphragmatic hernias of whom three lived long enough to undergo operations. One baby had an operation for oesophageal atresia with a tracheo-oesophageal fistula associated with a gastric perforation when he was 2 days old. Four patients were treated with peritoneal dialysis. Two survived the immediate crisis, but one of these died 15 days later from respiratory disease.

Miscellaneous (n=6)—Two of these babies had circulatory collapse associated with idiopathic respiratory distress syndrome, one with cardiac tamponade caused by a large haemopericardium. One baby had rhesus hydrops with a cord haemoglobin concentration of only 30 g/l and had had several cardiac arrests during exchange transfusions. One baby had renal cystic dysplasia, and in two the cause of the acute renal failure was not clear although one of them was born at 26 weeks' gestation to a mother who was in end stage chronic renal failure. This baby became anuric when 3 days old. Two of the four babies who were treated with peritoneal dialysis survived.

TREATMENTS

Treatment of hyperkalaemia—Five babies were treated with the ion exchange resin calcium polystyrene sulphonate made up as a slurry and given rectally in a dose of 1 g/kg three or four times daily. The consistency of the slurry made administration difficult and it was poorly retained by most babies. Calcium polystyrene sulphonate can set to become a solid plug, which may cause partial obstruction and bowel distension. Within 24 hours of its use two babies had died, and three were being dialysed.

Acute cardiac arrhythmias were treated with intravenous boluses of 10% calcium gluconate. The babies usually returned to sinus rhythm immediately, but it was not sustained. Three babies were also given soluble insulin 0·1 U/kg as an intravenous bolus while they were having intravenous dextrose infusions. All temporarily reverted to sinus rhythm, but the hypoglycaemia that was caused by this proved difficult to control because of the large volumes of intravenous dextrose that were needed to maintain normal blood glucose concentrations

Treatment of acidosis—All babies developed metabolic acidosis with base deficits of more than 10 mmol/l. They were treated with intravenous sodium bicarbonate 8·4% unless they also had respiratory acidosis, in which molar concentrations of trometamol were used. In no case were alkalis withheld because of fluid overload. The acid base balances improved of all the babies that were dialysed, although in four the base deficit remained greater than 10 mmol/l. All babies had problems in addition to their renal failure—for example septicaemia and hypotension—so the origin of the acidosis could not be clearly defined.

Control of blood pressure—Eighteen babies had their blood pressure monitored through an indwelling arterial catheter. Twelve of these received continuous dopamine infusions, compared with six of the 12 monitored by Dynamap (Critikon Inc, Tampa, Florida, USA). Analysis by the χ^2 test with Yates' correction showed that the use of direct pressure measurement did not influence the decision to use dopamine. In only two instances was it necessary to exceed an infusion rate of 10 µg/kg/minute. Acute falls in blood pressure were treated with 'walking donor' blood transfusions of 10–20 ml/kg.

Peritoneal dialysis—Table 3 shows a comparison of the 12 babies who were dialysed with those who were not. The significant differences in birth weight ($p<0·02$) and gestational age ($p<0·05$) reflect the fact that most of those dialysed were born at full term with serious surgical problems.

The main indications for peritoneal dialysis were: failure of medical treatment of hyperkalaemia, cardiac arrhythmias, and severe fluid overload with intractable cardiac failure. The two infants who developed resistant hypoglycaemia after intravenous insulin infusions achieved normal blood glucose concentrations as soon as peritoneal dialysis was started.

The dialysis fluid (Dianeal 137 with 1·36% glucose, Travenol Laboratories Ltd, Norfolk) was first warmed to 37°C. To make it easier to insert the peritoneal catheter, the abdomen was distended with about 50 ml/kg of the dialysis fluid taking care not to compromise ventilation. Cycle volumes were 30 ml/kg, repeated each hour; the fluid was run in rapidly by gravitational flow over five to 15 minutes, allowed to remain for 20–30 minutes, and then drained during the remainder of the hour. Dialysis cycles were repeated less often as urine output resumed. Once the serum potassium had fallen below 5·0 mmol/l, 4·0 mmol potassium chloride were added to each litre of dialysate.

Dialysis catheters were removed after the diuretic phase of recovery from acute renal failure had been completed. Two infants had further rises in serum urea concentrations (to 29·2 and 38·4 mmol/l, respectively) for three and four days after removal of their dialysis catheters. Urine output, however, was maintained and serum potassium concentrations remained below 6·0 mmol/l.

Commercially available catheters (Wallace 14147, Wallace Ltd, Colchester, Essex)) were used for most babies, but they were unsuitable for the smallest (minimum birthweight 620 g) because of the length of catheter needed within the peritoneal cavity. For such cases we found that chest drain catheters (Vygon 625·10, Vygon, Ecouen, France), which we modified by cutting extra holes in the sides, were a satisfactory alternative.

The only complications were minor fluid seepage around the peritoneal catheter, blockage of the catheter, and (in one infant) herniation of omentum through the abdominal wall during removal of a blocked catheter. No infant developed peritonitis. One showed biochemical deterioration during dialysis associated with a second episode of septicaemia;

Table 3 *Comparison of those babies who were dialysed and those who were not*

	No of babies	*Mean (SD) gestation (weeks)*	*Mean (SD) birth weight (g)*	*Median (range) age at onset of renal failure (days)*	*Median (range) age at death (days)*	*Mean (SD) peak urea concentration (mmol/l)*	*Mean (SD) peak potassium concentration (mmol/l)*
Babies dialysed	12	33·0 (5·1)	2070 (860)	4 (2–31)	13 (5–33)	18·3 (10 0)	8·0 (2 0)
Babies not dialysed	18	2[illegible]·4 (3·5)	1300 (610)	3 (2–57)	4 (2–60)	16·6 (10·5)	8 1 (2·6)

Table 4 *Timing of giving tolazoline and association with onset of renal failure*

	No of babies	*Median (range) at time of use (days)*	*Median (range) age at onset of renal failure (days)*
All babies	15	2 (1–3)	2 (1–14)
Haemorrhage or asphyxia, or both	8	1·5 (1–2)	2 (2–5)
Surgical problems	5	2 (2–3)	2 (2–4)
Others	2	2 (1–3)	8·5 (3–14)

culture of peritoneal dialysis fluid showed no organisms. It was not our practice to add antibiotics to the dialysis solution as a routine.

Despite the technical success of peritoneal dialysis, only three of the 12 treated infants survived. Two others were successfully dialysed but ultimately died: one was dependent on the ventilator, but found to have renal cystic dysplasia on ultrasound examination. After discussion with the parents, ventilation and dialysis were discontinued. One other infant who was dialysed for five days because of postoperative complications died 15 days later from unrelated respiratory disease.

Drugs used before the onset of acute renal failure—Fifteen babies were given tolazoline, all within the first 3 days of life, one having a second course on day 5 (table 4). Doses of 1–4 mg/kg were given as intravenous boluses followed by continuous infusions of 2–5 mg/kg/hour. One baby inadvertently received a 15 mg/kg bolus and an infusion rate of 10 mg/kg/hour. Twelve of the 15 babies were treated with intravenous dopamine infusions at rates sufficient to maintain normal systemic blood pressure (2–15 μg/kg/minute), and 13 were given neuromuscular blocking agents to facilitate mechanical ventilation. Four babies received indomethacin, but this was not associated with their renal failure.

Discussion

The diagnosis of renal failure in the newborn is not straightforward, as it is usually not the baby's only problem. For these reasons we looked at a combination of three criteria associated with acute renal failure: anuria or oliguria, uraemia, and hyperkalaemia.

For the diagnosis of anuria and oliguria we relied on the accuracy of our nursing records in which it is recorded 8 hourly whether the baby has passed urine or not. Oliguria was diagnosed when the nurses expressed concern over the frequency and amount of urine passed.

Other causes for a raised serum urea concentration should be considered. It is unlikely that these babies were dehydrated, all received conventional intravenous fluid regimens during their first days of life and were clinically assessed at least twice a day. Twenty two developed acute renal failure within the first 5 days of life.

Excessive protein loading was also an unlikely explanation for raised serum urea concentrations, only three babies ever received milk feeds, and only seven received intravenous amino acids (Vamin 9 glucose, KabiVitrum Ltd, London) up to a maximum of 2·5 g/kg/day.

In only one instance was a raised urea concentration the only feature of renal failure. The baby was born at 27 weeks' gestation weighing 800 g, and had severe perinatal asphyxia (Apgar score 1 at 5 minutes). Because of increasing oedema she was treated with frusemide on day 3. The serum urea first rose above 10 mmol/l on day 5, reaching a maximum of 25·1 mmol/l on day 8.

The cases reported are a highly selected group. All were extremely ill, and those who survived were unlikely to have done so without dialysis. The exact cause of death could not be determined in most cases; the contribution of acute cardiac arrhythmias caused by hyperkalaemia in a baby with overwhelming septicaemia, for example, makes it difficult to assess.

As far as we are aware no other babies developed acute renal failure during the study period. Other babies may have had transient renal insufficiency as part of the idiopathic respiratory distress syndrome,[11 12] but this required nothing more than a period of fluid restriction. Others might possibly have developed acute renal failure if they had survived long enough.

Treatment of hyperkalaemia with drugs was disappointing. Intravenous calcium gluconate and insulin were almost immediately effective in stopping cardiac arrhythmias but only in the short term. Calcium polystyrene sulphonate was difficult to use and seemed to give little benefit.

We have found peritoneal dialysis to be a safe procedure without serious complications. It was technically successful in all cases, the 25% survival rate being a reflection of the babies' conditions before dialysis rather than a problem with the dialysis itself. In babies with cardiac arrhythmias dialysis was successful after conventional treatment had failed to maintain sinus rhythm. It is possible, therefore, that earlier use of dialysis as prophylaxis against hyperkalaemic arrhythmias could have increased the rate of survival. This raises the ethical dilemmas of offering dialysis to sick neonates; most babies already had a poor prognosis before the onset of their renal failure and dialysis would only have delayed their deaths. We suggest that those babies who have had severe perinatal asphyxia or who develop a large intraventricular haemorrhage with cortical extension and severe neurological abnormality should not be offered dialysis if they develop acute renal failure shortly after birth.

Tolazoline is an α adrenergic blocking agent that also has a direct action on vascular smooth muscle to produce dilatation. It is used in infants with severe hypoxaemia associated with pulmonary hypertension and right to left vascular shunting.[5 6] Tolazoline also has an excitatory action on the myocardium and may cause cardiac arrhythmias.[13] Because it is excreted largely unchanged by the renal tubules[14] modification of the dose may be necessary when renal function is impaired.

The association between the use of tolazoline and the onset of renal failure appeared close, but it was used only in extremely sick infants who already had other reasons to develop acute renal failure. It is impossible to say whether the use of tolazoline was responsible for any of these babies developing acute renal failure, but its hypotensive effect may have further compromised their already impaired renal function It is also possible that tolazoline may have precipitated some of the cardiac arrhythmias. It should be stated, however, that many more babies received tolazoline during the study period and did not go on to develop acute renal failure.

Since 1981 most babies were treated with tolazoline and also received intravenous infusions of dopamine. The dose was titrated against blood pressure, aiming to raise the systolic pressure above 50 mm Hg. At low infusion rates (2–5 μg/kg/minute), dopamine stimulates dopamine receptors in the renal arteries causing them to dilate and so increase renal blood flow.[15] At higher rates of infusion (>10 μg/kg/minute), however, stimulation of α adrenoreceptors causes an increase in vascular resistance and thus a fall in renal blood flow.[16] In the study group, there were wide variations in dopamine infusion rates (2–15 μg/kg/minute). It seems that dopamine did not have a beneficial effect on renal function in this group of babies.

In conclusion, there has been an increase in the number of babies developing acute renal failure during the past few years reflecting improved resuscitation of extremely sick infants and increased survival from the idiopathic respiratory distress syndrome,[4] although increased awareness of the possibility of renal complications may also play a part.

Peritoneal dialysis is a safe and effective way to manage acute renal failure in the newborn. We suggest that if the baby is thought to be a suitable candidate, dialysis should be started before cardiac arrhythmias develop or immediately after any emergency treatment for hyperkalaemia.

Tolazoline should be used with caution in infants with renal impairment as it is excreted by the kidneys, compromises renal circulation, and may precipitate cardiac arrhythmias. The use of dopamine to maintain blood pressure after giving tolazoline needs to be studied more critically and compared with the effects of plasma and other drugs.

We thank Dr AJ Barson for his help with this paper and colleagues at the neonatal medical and surgical units, St Mary's Hospital, Manchester, for allowing us to report their patients The practical help of Dr RJ Postlethwaite in the management of some patients is acknowledged

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Accepted 5 July 1988

Archives of Disease in Childhood, 1988, **63**, 1377–1381

Skin to skin contact for very low birthweight infants and their mothers

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SUMMARY Separation between mothers and very low birthweight infants is often prolonged with subsequent psychological distress, behaviour problems, and lactation failure. Babies as small as 700 g, who no longer require oxygen, can be safely and enjoyably held naked, except for a nappy, between the mother's breasts for up to four hours a day. We have carried out a randomised trial among babies less than 1500 g. Seventy one infants were randomised. In 35, the mother was helped to hold her baby in skin to skin contact and encouraged to do so whenever she visited the baby. In 36, the mother was encouraged to handle her baby but without skin to skin contact. Mothers using skin to skin contact lactated for four weeks longer on average than the control group. At 6 months of age the infants who had skin to skin contact cried significantly less than the control group. Skin to skin contact can safely and enjoyably be offered to very low birthweight infants especially in developing countries where the mother's lactation is vital.

The decrease in perinatal mortality over the last 40 years has been accompanied by the rigorous precautions against sepsis that were thought to justify separation of mother and baby, and this has been particularly true with very low birthweight infants (<1500 g). Such infants may stay in a special care baby unit for three months and visiting by parents may be limited by the distance from home to hospital. A Perspex incubator forms an additional barrier between parent and baby for weeks or months. There has been much concern about the psychological consequences of prolonged separation on small babies and their mothers.

The value of early skin to skin contact in improving communication between mothers and full term infants has been highlighted by Klaus *et al.*[1] Since their pioneering work many other studies have been carried out to evaluate the effects of early separation or, conversely, extra contact, on mother and baby.[2–8] While results have been somewhat variable, reviews have concluded that separation does have some deleterious effects on the relationship, the frequency and duration of lactation, and the mother's feelings of confidence in being able to cope with her baby at home. Such effects have been shortlived, however, and within a few weeks or months of reunion after separation are no longer seen.

Skin to skin contact for very low birthweight infants was pioneered in Bogota, Colombia by Rey and Martinez.[9] Because of a high rate of death and abandonment in their large maternity hospital each preterm mother was encouraged to nurse her baby, however small, next to her skin between her breasts. The infants were in the head up position to minimise the risk of aspiration. This has come to be known as 'kangeroo baby care' and has received considerable interest among neonatal nurses.[10] No randomised trials have been published on this type of close physical handling for such small and fragile infants.

Pilot studies showed us that stable infants as small as 700 g could be safely held skin to skin and that mother and baby seemed to enjoy the experience. If flexion of the infant is avoided, oxygenation is well maintained. A hat is advised for the smallest infants to maintain temperature. Mothers have made comments such as 'Now I feel he's getting to know me' and 'I feel like a mummy now' Encouraged by these positive results we planned an objective evaluation

This paper reports the results of a randomised controlled trial of skin to skin contact for very low birthweight infants and their mothers to test the following hypotheses: (1) early skin to skin contact improves the mother's confidence and positive feelings towards her baby when she takes the baby home and when the baby is 6 months old; (2) early skin to skin contact influences the infant's behaviour at 6 months of age; and (3) early skin to skin contact prolongs lactation.

Patients and methods

All infants in the Hammersmith Hospital neonatal unit were eligible for the study if they weighed less than 1500 g, had stable breathing with no oxygen requirement, and if at least one parent spoke fluent English. Stable infants were not excluded if they had congenital abnormalities such as hydronephrosis or scoliosis, nor if they had intracranial lesions such as periventricular leukomalacia or ventricular dilatation.

Infants meeting these requirements were identified by the nursing staff and entered into the trial. Each infant was randomised by a nurse opening sequentially a numbered sealed, opaque envelope, which contained a sheet of paper allocating the infant to either (a) skin to skin contact or (b) normal handling. The envelopes had been prepared by medical staff, AW or GH, in balanced blocks of six.

MANAGEMENT OF TRIAL GROUPS

If the infant was randomised to skin to skin contact, one of the nurses presented the idea of skin to skin contact to the mother, showing pictures if necessary. It was explained that it was a safe and enjoyable way to hold and get to know her baby but without any proven lasting benefit. Initially the mother was helped to position her baby inside her dress and between the breasts (figure) with a cardiac or respiration monitor attached. After the first two occasions, the mother was encouraged to hold her baby in this position whenever she came to visit and to continue this close contact for the rest of the time her baby was in Hammersmith Hospital and later

If the infant was randomised to normal contact, the mother and baby had the same amount of support and help as the skin to skin contact group The mother was encouraged to visit as much as she liked and helped to take her baby out of the incubator for a cuddle. However, baby and mother remained clothed. Care was taken that the normal contact group would have no less attention from the nursing staff for talking listening, questions and answers.

In cases of twin pregnancy the first twin who was ready to enter the trial was randomised as described above. If the other twin became eligible for the trial, the new trial entrant was allocated the same handling as the first twin as it was felt that it was unacceptable to ask a mother to handle one twin differently from the other one. If an infant in the trial became unwell, the trial was discontinued until the infant was stable again. This applied equally to both handling groups.

Figure *An infant girl, born at 27 weeks' gestation and weighing 880 g, held in skin to skin contact by her mother at 2 weeks postnatal age*

Each time the mother visited, a record was kept of the duration of the visit, normal (that is, clothed) contact, and skin to skin contact.

MEASUREMENT OF OUTCOME

When the infant was about to be discharged from Hammersmith Hospital, either to go home or back to the referring hospital, the mother was given a questionnaire. The mothers were asked to rate themselves on a six point scale. The questions covered confidence looking after the baby, knowing the baby well, feeling optimistic about the baby, being depressed, feeling detached from the baby, and feeling supported in looking after the baby. Each mother was also asked if she had thought at any time that her baby was going to die.

All infants in the trial were seen in the routine neonatal follow up clinic at 6 months of age (uncorrected for prematurity). Again, mothers were asked to answer a questionnaire on feelings about the baby on a six point scale The questions concerned: feeling detached from the baby, knowing what the baby wants, whether the baby expects to be carried around, whether the baby is contented, feeling annoyed with the baby, whether the baby is easier to look after than she had thought in hospital, support in looking after the baby, being worried that something will still happen to the baby, and feeling that the baby's behaviour has completely caught up with full term babies. Each mother was also asked when she thought her baby was really hers.

Duration of lactation was determined by history from the mother at discharge, or at six months. If the mother was still lactating at six months, the duration of lactation was determined at the nine or 12 month routine visit.

At six months the parents were asked to keep a 48 hour diary of the infant's behaviour. Duration and frequency of sleeping, feeding, being held, and playing were recorded by the parents to the nearest 15 minutes. Playing was defined as the infant being awake and taking notice of the surroundings but without crying, being held, or fed. Duration and frequency of crying were recorded to the nearest five minutes. When the parents were unable to come to the neonatal follow up clinic, the questionnaires and diaries were sent and returned by post. In 12 cases, a home visit by AW was necessary to complete the information. Follow up data were obtained for all surviving infants.

Before the randomised trial started, we piloted the questionnaires and the diary with mothers of very low birthweight infants. Minor modifications to the original layout were made as a result of the pilot study.

SAMPLE SIZE

We previously had found 32–33% of mothers of very low birthweight infants were still lactating at six weeks. To have an 80% chance of detecting a doubling of this proportion to 65% (at $p<0{\cdot}05$) would require 36 subjects in each group. We aimed to recruit 80 infants. Over an 18 month period, August 1985–February 1987, 71 infants were entered in the study. This represents about half of all the very low birthweight infants admitted to the Hammersmith Hospital neonatal unit during that period. The reasons for the remaining infants not being entered were: prolonged respiratory problems, early transfer back to the referring hospital, early neonatal death, and neither parent speaking fluent English. Because of the number of multiple pregnancies and four deaths, 71 infants recruited to the study gave a total of 63 mothers available to give a lactation history.

Statistical analysis was carried out on a Perkin Elmer 3220 computer using Minitab statistical packages. Where data had a Gaussian distribution and similar variances, means were compared using the unpaired Student's t test. Where data did not have a Gaussian distribution, comparisons were made using the Mann-Whitney U test and χ^2 test.

The study was approved by the Hammersmith Hospital research ethics committee.

Results

Table 1 shows the characteristics of the infants and mothers at entry to the trial. Thirty five infants were randomised to the group with skin to skin contact and 36 to group with normal handling. There was no significant difference in birth weight, gestational age, sex, Apgar scores, caesarean section rate, parity, previous neonatal death, ethnic group, social class, or lack of partner support. Thus the two groups were similar for many important factors that could affect the mother's relationship with her child in the first few weeks. The infants entered the trial on average on the 16th day (there was a range from the first to 61st day for the group with skin to skin contact and from the the first to 66th day for the group with normal handling) The numbers of mothers originally wishing to breast feed were similar (24 (77%) in the group with skin to skin contact and 26 (81%) in the group with normal contact). Those in the group with skin to skin contact remained at Hammersmith for a median 30 days (range 5–83 days) and those in the group with normal contact remained a median 37 days (range 5–78 days).

Table 2 shows details of the visiting. Average

Table 1 *Characteristics of infants at entry to trial*

	Group with skin to skin contact	*Group with normal handling*
No of infants	35	36
Male/female	21/14	14/22
Singleton	26	27
Mean (SD) birth weight (g)	1152 (220)	1135 (263)
Range	560–1500	630–1500
Mean (SD) gestational age (weeks)	29·1 (2 3)	29·5 (2 3)
Range	26–35	25–36
Mean Apgar score at 1 minute	5·6	5 5
Caesarean section	23	23
Primiparous	21	19
Previous neonatal death	2	2
White	26	24
Asian	5	8
Afro-Caribbean	4	4
Unsupported mother	2	4
Intention to breast feed	24	26

Table 2 *Handling and visiting by parents in the neonatal unit during the trial*

	Group with skin to skin contact (n=35)	*Group with normal handling (n=36)*
Mean (SD) visiting/day (hours)	2·1 (0·8)	2·2 (0·9)
Range	0·7–3·9	0·7–11·0
Median time left in incubator while mother visited (hours)	0·1	0·1
Range	0–2·0	0–5·9
Mean (SD) time touched or cuddled with clothes on (hours)	1·4 (0·7)	1·8 (1·0)
Range	0·2–3·4	0·5–5·2
Median time skin to skin contact (hours)	0·6	—
Range	0–1·5	

Table 3 *Behavioural findings in the infants at 6 months of age*

	Group with skin to skin contact (n=35)	*Group with normal handling (n=36)*
Mean (SD) hours sleeping/day*	13·6 (2·3)	13·4 (2·3)
Mean (SD) hours feeding/day*	2·5 (1·1)	2·5 (0·9)
Mean (SD) hours being held/day*	3·0 (1·3)	3·0 (1·4)
Mean (SD) hours playing/day*	4·5 (1·8)	4·5 (1·8)
Median (range) minutes crying/day†	25 (0–100)	38 (5–140)

*Gaussian distributions no difference between means was significant at $p<0·05$ by Student's *t* test

†Non-Gaussian distribution Mann-Whitney U test $p=0·0422$.

visiting was just over two hours a day, most of it spent holding the infant clothed. Visiting time was limited by the long distance from some homes to the hospital, lack of a family car, the needs of older children at home, and by illness of the mother. The group with skin to skin contact had, on average, 36 minutes per day of skin to skin contact. Breast feeding time was not counted as skin to skin contact time. Skin to skin contact was declined by five mothers, three of them Asian and two white, but these infants remained in the group with skin to skin contact for analysis of outcome in order not to violate the randomisation. There was no difference overall between the two groups in total visiting time.

Temperature instability was not a problem during skin to skin contact. The trial had to be discontinued temporarily in six infants in each group because of apnoeas, necrotising enterocolitis, or sepsis. Two infants died in each group between entering the study and reaching 6 months of age. Two infants died of septicaemia, one had necrotising enterocolitis, and one had a sudden infant death. This underlies the high risk nature of the population we are dealing with.

When questionnaires at discharge and at six months were analysed, there was no significant difference between the two groups on any of the six point psychological scales. It is noteworthy that 48 (67%) of the mothers overall thought that at some time their baby was going to die, and that 30 (42%) did not feel that the baby was really theirs until he or she was home.

Table 3 shows the behavioural findings from the diary kept when the infants were 6 months of age. The duration of sleeping, feeding, being held, and playing were almost identical in the two groups. Median duration of crying was 25 minutes per day in the group with skin to skin contact and 38 minutes per day in the group with normal handling. This difference was significant by the Mann-Whitney U test ($p=0·0422$).

Mean duration of lactation in the group with skin to skin contact was 9·2 weeks (median 7 weeks) whereas, in the group with normal handling, mean duration of lactation was 5·1 weeks (median 3·5 weeks). The results for the two groups are significantly different (Mann-Whitney U test, $p=0·0167$). Furthermore, 17 out of 31 mothers (55%) in the group with skin to skin contact lactated for more than six weeks; this compares with only nine out of 32 (28%) in the group with normal handling (χ^2 $p<0·02$).

Discussion

The intervention in this randomised trial consisted of presenting and encouraging early skin to skin contact in a busy regional neonatal intensive care unit where mothers are already encouraged to visit whenever they like, siblings can visit, and there is a generally relaxed and supportive atmosphere. Introducing skin to skin contact did not significantly prolong total visiting time. Apart from the five mothers who declined, each mother and baby seemed to enjoy skin to skin contact, but we were unable to detect any psychological advantage when the baby was discharged from our hospital or at 6 months of age. In contrast to the study by Klaus *et al*,[1] our trial involved infants under 1500 g rather than full term infants and all our mothers had a lot of other forms of emotional support as well as unlimited access to see and handle their infants (which was not the case in the study of Klaus *et al* in Cleveland, Ohio). We conclude that early skin to skin contact does not seem to be more effective than other forms of contact and general support in giving mothers of very low birthweight infants longer term confidence and positive feelings.

On average the very low birthweight infants with skin to skin contact, aged 6 months, cried for 13 minutes per day less than the group with normal handling. Many parents would rate this a valuable advantage. Regular skin to skin contact may give the infant security and tranquility, which is reflected in less crying subsequently. Infants who had had early skin to skin contact did not demand to be held more than the control group at 6 months of age and were not carried around more by their mothers.

The four week increase in duration of lactation and the proportion of mothers lactating for more than six weeks is an important finding and is in agreement with De Chateau and Wiberg's trial of skin to skin contact for full term infants.[2] Presumably an average of 36 minutes a day of close physical contact between the baby and both breasts is enough to increase the secretion of prolactin. Even in developed countries mother's milk is widely regarded as the most suitable food for very low birthweight infants.[11] It can be given raw to preserve its protective substances and supplements of sodium and minerals can be given as necessary. If the mother is able to maintain her lactation for six weeks then there is a good chance that she will be able to breast feed the baby at home. In developing countries, mother's milk is much more important, literally life saving, because of the relatively high cost of milk formulas and the risk of diarrhoea from contaminated milk.[12] In the Third World, the use of 'kangaroo baby care' may be an important way of maintaining the mother's precious lactation.

We are grateful to the nursing staff of the Hammersmith Hospital neonatal unit and to the parents and babies studied. Dr Acolet was supported by a grant from Foundation pour la Recherche Medicale, Paris

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Accepted 16 May 1988

Archives of Disease in Childhood, 1988, **63,** 1382–1385

Mother's choice to provide breast milk and developmental outcome

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SUMMARY The association between a mother's choice to provide breast milk and her baby's developmental status at 18 months post term was investigated in 771 low birthweight infants from five centres. Babies whose mothers chose to provide milk had an 8 point advantage in mean Bayley mental developmental index over infants of mothers choosing not to do so. A 4·3 point advantage remained after adjusting for demographic and perinatal factors. A similar finding was derived using a fundamentally different and questionnaire based test (academic scale of Developmental Profile II). Whether this significant residual developmental advantage relates to parental factors or to a beneficial effect of human milk itself on brain development has important implications for the nutritional management of premature babies.

Later developmental status of children who were breast fed has been reported to be higher than in those fed artificially.[1-4] These two groups, however, differ significantly in social, demographic, and educational factors that are known to be related to developmental scores. Silva *et al*,[5] in a study where breast fed children were matched with non-breast fed controls, found no significant developmental advantage for those breast fed for varying lengths of time. Rodgers,[6] analysing data from the National Survey of Health and Development (1946 cohort), found that after adjusting for social and demographic factors those children who had been entirely breast fed had a small, significant advantage on tests at 8 and 15 years. Using data from the Child Health and Education Study five-year follow up, Taylor and Wadsworth found a positive correlation between duration of breast feeding and performance in tests of vocabulary and visuomotor coordination, which persisted after similar adjustment.[7]

Low birthweight infants are a special population. They are a high risk group for impaired development. Moreover, if the mother chooses to breast feed she may have to express her milk, manually or mechanically, for a prolonged period until her infant is able to feed from the breast. A previous analysis of data from the cohort studied here has identified the factors independently related to a mother's choice to breast feed her low birthweight infant.[8] In this study we have explored the relationship between the mother's intention to breast feed her preterm infant and the baby's developmental status at 18 months post term.

Patients and methods

Babies under 1850 g at birth, admitted to the special care baby units in Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield between January 1982 and March 1985, were entered into four parallel trials of preterm infant feeding, details of which are published elsewhere.[9] Mothers chose whether or not they wanted to provide breast milk for their infant within 72 hours of delivery. In this study we have examined how this choice relates to development (though it should be emphasised that this is an epidemiological, non-random comparison and is not one of the randomised feeding trials cited above). Detailed information was collected on the family structure, social class, and mother's education level; and also on the pregnancy, labour, delivery, and the neonatal period.

Social class was coded using the Registrar General's classification based on the occupation of the income providing parent or on the father's occupation if both parents were earning, and with class 3 subdivided into non-manual and manual. Mother's education was coded as follows: 1=no educational attainments, 2=up to four passes for the certificate of secondary education (CSE), 3=any 'O' levels or more than four CSEs, 4=any 'A' levels, and

5=degree or higher professional qualifications. Birth rank was defined as the child's birth order in the surviving children of the family, with infants from multiple births assigned equal rank Mode of delivery was categorised as caesarean or vaginal

The 834 surviving infants were invited to an 18 month follow up examination. Infants from the four East Anglian centres were seen by RM; RP supervised follow up in Sheffield.

Two different tests of mental ability were administered: the Bayley mental scale[10] and the academic scale of Developmental Profile II.[11] The Bayley mental scale was scored on items presented to the child by the examiner, the mental developmental index being calculated from the raw score. A questionnaire to the care giver was used for the academic scale of Developmental Profile II, from which an IQ equivalent was calculated. The child's age from expected date of delivery (that is, chronological age minus the difference between date of delivery and term) was used in calculating the scores.

The Bayley mental scale, like most tests of mental ability in young children, requires age appropriate manipulative skills; therefore in children with cerebral palsy the score does not usually reflect the level of intellectual ability. At this age the academic scale of Developmental Profile II is based on items which are largely independent of fine manipulative skills. Results from 50 infants with cerebral palsy are therefore included in analyses of IQ equivalent, but not in analyses of the mental developmental index.

Of the 834 infants surviving to 18 months from expected date of delivery, the Bayley mental scale was successfully administered in 746 cases (89%), the academic scale of Developmental Profile II in 758 cases (91%), and one or both tests in 771 cases (92%).

Student's *t* test and multiple regression analysis were used for statistical analysis. Social class and mother's education were grouped to give a linear relationship with the mental developmental index and IQ equivalent (see footnote to table 2).

Results

Table 1 shows the mean scores at 18 months for the mental developmental index and IQ equivalent, both of which were significantly higher for the group of infants whose mothers chose to provide breast milk, with an advantage of 8 points in mental developmental index and 7 points in IQ equivalent.

From our previous analysis, factors independently related to the mother's decision to provide breast milk were mother's education level and age, baby's sex, birth rank (first child or not), and mode of delivery (caesarean versus vaginal), and whether the mother was a single parent.[8] Other factors related (though not independently) to the mother's choice to provide breast milk and found from prior analyses to be significantly related to developmental scores were social class, gestation, and birth weight. The number of days for which the baby required ventilation was also taken into account here because the baby's illness might affect both feeding preference and the child's developmental outcome. All these factors were analysed for association with the mental developmental index and IQ equivalent, using multiple regression with the mental developmental index and IQ equivalent as dependent variables.

After adjustment for all these variables, a significant advantage of 4·3 points (p<0·01) remained for babies whose mothers chose to provide breast milk. Mode of delivery and having a single parent mother were not associated with mental developmental index and when these two non-significant factors were removed from the model, the 4·3 point advantage (above) remained (p<0·005). Table 2 shows the regression coefficients when only factors significantly related to outcome are included in the analysis. (The negative regression coefficient for gestational age in table 2 is due to the use of a birthweight cut off to select subjects for this study. All infants born after 34 weeks' gestation are small for gestational age; with birth weight in the equation the disadvantage of inappropriate birth weight for gestation becomes evident.)

Table 1 *Mother's choice to provide breast milk and mean scores for Bayley mental developmental index and IQ equivalent at 18 months post term*

	Bayley mental developmental index		*IQ equivalent (from Developmental Profile II)*	
	No of babies	*Mean (SE) score*	*No of babies*	*Mean (SE) score*
Mother chose not to provide breast milk	227	95·4 (1·2)	245	101·5 (1·1)
Mother chose to provide breast milk	469	103·3 (0·9) p<0·001	513	108·3 (0·8) p<0·001

Table 2 *Regression analysis including factors significantly associated with developmental scores at 18 months*

Factor	*Bayley mental developmental index**	
	Regression coefficient (SE)	*p Value*
Mother chose to provide breast milk	4·3 (1·5)	<0·005
Social class†	−4·0 (0·7)	<0·0001
Days of ventilation	−0·7 (0·1)	<0·0001
Female infant	5·1 (1·3)	<0·0005
Gestational age (weeks)	−1·2 (0·3)	<0·0005
Birth rank‡	4·2 (1·4)	<0·005
Birth weight (per 100 g)	0·7 (0·3)	<0·05
Mother's education§	5·0 (2·7)	<0·05
Mother's age >20 years	5·8 (2·3)	<0·05

*Cases of cerebral palsy excluded
†Social class was categorised as: social class 1 or 2, social class 3 non-manual, social class 3 manual, or social class 4 or 5
‡Birth rank was categorised dichotomously as first child or subsequent child
§Mother's education level was categorised as 1, degree or higher professional qualifications; 2, all other levels.

A similar advantage in IQ equivalent of 4·4 points ($p<0·005$) was found after adjustment for the same factors.

Discussion

A low birthweight infant whose mother chose to provide breast milk had an 8 point advantage in Bayley mental scale score by 18 months, over one whose mother chose not to do so. It might be suggested that this advantage is explained by social and demographic influences. Even after adjusting for these, however, a greater than 4 point difference remained. It is interesting that the same advantage was found in IQ equivalent, a fundamentally different test. Our analysis (table 2) shows that this is similar to the advantage seen for being a first child, being female, or belonging to a higher social class category, when other factors are held constant.

In term infants, comparable studies have yielded conflicting results,[5 7] though our findings are broadly in agreement with those of Rodgers[6] and Taylor and Wadsworth.[7] (Interestingly, Rodger's report on the 1946 birth cohort relates to a time when high social class was not strongly associated with breast feeding.) Low birthweight infants however, are a special population. The baby's condition can cause considerable parental anxiety and disruption of family life. The mother's milk may have to be expressed until her baby is able to suck. It is likely, therefore, that mothers who breast feed term infants are a different group from those who provide milk for their preterm babies.

It is possible that our failure to 'adjust out' the advantage seen in babies whose mothers chose to provide breast milk was due to some extent to our failure to identify all relevant demographic factors, though a wide range of such factors were considered—the most important being social class and mother's education. This problem could have been compounded by unavoidable 'measurement error' in the determination of factors like social class.

Alternatively we have considered the possibility that fresh maternal milk might contain a factor or factors, hitherto unrecognised, which promote brain growth or maturation in the period of rapid growth preterm. Human milk contains a wide range of hormones and growth promoting factors, which have never been explored in relation to early neurological development.

Finally, it is possible that the advantage is related to the mother's decision to provide milk, rather than to the consumption of breast milk itself. For instance, her choice could be a reflection of her level of concern for the infant's welfare and perception of her maternal role, which would later influence her interest in stimulating and facilitating her baby's developmental progress. Thus a wish to provide breast milk could be seen as an aspect of 'parenting', that was at least partly independent of social class or educational status.

An important question from these data is whether staff in the neonatal unit should actively encourage provision of mother's milk for preterm infants on the grounds that it might improve developmental outcome. Currently, there is controversy over the use of human milk, in the light of mounting evidence that it may not meet the special requirements of infants born preterm. Information on whether or not breast milk itself exerts a significant effect on brain development would be critical in this debate. Analysis of data from our cohort is being undertaken to provide further evidence concerning the possible neurodevelopmental effects of preterm milk; on present information, such effects cannot be dismissed.

If, however, the developmental advantage observed here was not due to nutritional factors, it is of note that this advantage could not be 'adjusted out' in a regression model which included social class and mother's educational status. In that case our findings would have implications for the design of research into preterm infant feeding. For example, in a non-randomised study comparing the effect of mothers' milk with another diet on later psychometric scores, adjustment for group differences in standard demographic and social factors would not be effective in eliminating confounding (non-nutritional) effects on the outcome response.

Individual developmental scores at 18 months have limited predictive value for future mental ability, but group mean scores, as presented here, are likely to be more predictive. In a planned future study of this cohort, we will determine whether the early developmental advantage of infants whose mothers chose to provide milk persists, decreases, or even increases later in childhood

We gratefully acknowledge the help and cooperation of the paediatricians in Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield, and Farley Health Products Limited for financial help

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Accepted 28 April 1988

Archives of Disease in Childhood, 1988, **63,** 1386–1398

Short reports

Neonatal hypoglycaemia—the controversy regarding definition

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SUMMARY Major paediatric textbooks and the views of neonatologists in the United Kingdom were surveyed to establish a definition of neonatal hypoglycaemia. The definiton ranged from a glucose concentration of <1 mmol/l to <4 mmol/l. Hypoglycaemia is recognised to cause neurological sequelae and yet there is no accepted definition of the lower limit of normality for circulating blood glucose concentrations.

There are few areas in neonatology that are as controversial as the definition of hypoglycaemia. Hypoglycaemia is recognised as a common problem in newborn babies but its incidence is difficult to ascertain due to the controversy over definition. Sexson highlighted the issue in his paper where he showed that the incidence of hypoglycaemia in the 232 babies he studied would be 8·1% if hypoglycaemia was defined as a blood glucose concentration of <1·7 mmol/l or 20·6% if it was defined as <2·2 mmol/l.[1]

The aim of our study was to establish the degree of variation in the definitions of hypoglycaemia among paediatric textbooks and paediatricians in charge of special care nurseries in the United Kingdom.

Methods

The definition of hypoglycaemia, with reference to the glucose concentrations in whole blood in term babies who were born with a weight appropriate for gestational age and in babies who were preterm or small for gestational age, was ascertained (a) in 36 current paediatric textbooks and (b) from consultants in charge of special care nurseries with one or more intensive care cots. The names of the consultants were obtained from the Directory of Emergency and Special Care Units 1986,[2] and postal questionnaires were sent to them.

Results

The definitions of hypoglycaemia obtained from the review of the 36 textbooks of paediatrics are shown in fig 1. There was a very wide variation in the definitions given ranging from a glucose concentration of <1 mmol/l to <2·5 mmol/l with a modal value of <1·7 mmol/l for term babies of appropriate weight, and <1·1 mmol/l for babies who were preterm or small for gestational age.

There were 242 paediatricians identified from the Directory of Emergency and Special Care Units.

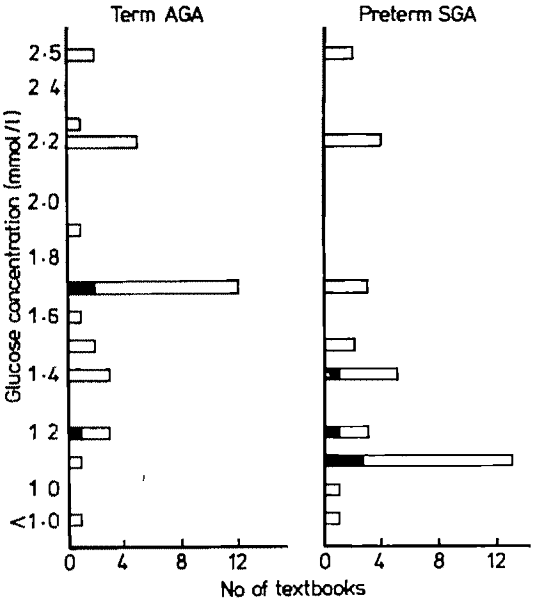

Fig 1 *The definition of hypoglycaemia obtained from a review of 36 current textbooks of paediatrics The shaded area of each histogram represents textbooks which define hypoglycaemia as two consecutive episodes of a blood glucose concentration below the given value AGA=weight appropriate for gestational age, SGA=small for gestational age.*

One hundred and seventy eight (73·5%) replied giving their definitions of hypoglycaemia and their responses are shown in fig 2.

There was an even greater controversy among the practising paediatricians whose definitions of hypoglycaemia ranged from a glucose concentration of <1 mmol/l to <4 mmol/l. The modal value for term babies of appropriate weight was <2·0 mmol/l and <1·1 mmol/l for babies who were preterm or small for gestational age. The response from paediatricians in charge of four or more intensive care cots was no more consistent than that from paediatricians in charge of less than four intensive care neonatal cots.

There were 41 special care nurseries from which two or more paediatricians replied. In these nurseries there were discrepancies in the definition of hypoglycaemia between paediatricians from the same unit in 25 (61%) cases. The discrepancy between their definitions ranged from 0·2 mmol/l to 1·8 mmol/l.

The site of sampling—that is, whether capillary, venous, or arterial blood was used for analysis of glucose concentration—was not included in the definition of hypoglycaemia by any of the textbooks reviewed nor by any of the paediatricians in our survey.

Discussion

Our results show that the definition of hypoglycaemia in the neonate continues to be a controversial and a confused issue. Not only is there no consistency in the definition between the paediatric textbooks, but of more importance there seems to be little agreement among neonatologists caring for the babies. Such discrepancy, which we have shown can occur even within the same nursery, must surely lead to confusion among junior medical and nursing staff and to inconsistency in the management of babies. There also appears to be a persistence of the belief that the brain of the infant who is premature or small for gestational age is more tolerant to low blood glucose concentrations than that of the full term normal baby.

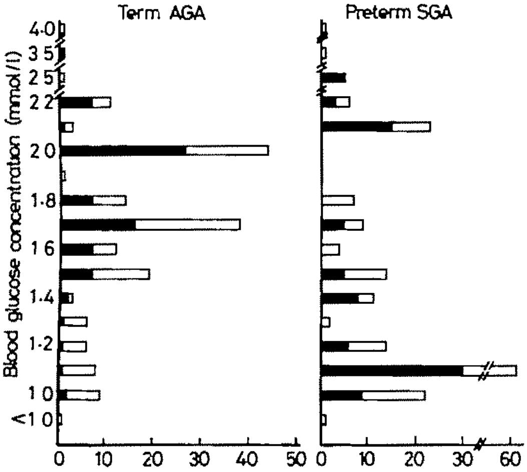

Fig 2 *The definition of hypoglycaemia given by 178 paediatricians The shaded area represents those paediatricians in charge of nurseries with four or more intensive care cots. AGA=weight appropriate for gestational age, SGA=small for gestational age*

The difficulty with the definition of hypoglycaemia is, however, understandable in view of the lack of reliable clinical signs in the neonate when the blood glucose concentrations fall, and in view of the continuing controversy over whether asymptomatic hypoglycaemia causes neurological damage.[3]

Previous definitions of hypoglycaemia have been based on the description of glucose concentrations in the blood, plasma, or serum in groups of newborn babies under various circumstances and the establishment of the range of values found.[1 4 5] Hypoglycaemia is then often defined as a glucose concentration less than one standard deviation below the mean value.[4] The limitations of this approach are most clearly shown by the discrepancy between various authors in the resulting definitions of hypoglycaemia. Srinivasan and colleagues for example, who measured plasma glucose concentrations in healthy term babies at varying ages, recommended that hypoglycaemia should be defined as a plasma glucose concentration of <2·2 mmol/l in the first 24 hours after birth and <2·6 mmol/l thereafter.[3] In contrast Heck and Erenberg, who similarly measured serum glucose concentration in healthy term babies at varying ages, recommended that hypoglycaemia be defined as <1·7 mmol/l in the first day after birth and <2·2 mmol/l thereafter.[6]

The range of concentrations of glucose obtained in a study of a population of babies is dependent upon many factors: (1) the presence of predisposing factors—for example, birth asphyxia, maternal diabetes, or being small for gestational age; (2) the physiological status of the baby at the time of sampling in relation to the method of feeding and the time from feeding to blood sampling; (3) whether venous, capillary, or arterial blood is obtained, and whether whole blood, serum, or plasma is used for the analysis; (4) the time between sampling and analysis and the technique of measurement used (whether Dextrostix, Reflolux, glucose oxidase technique, etc); and (5) the methods used to prevent glycolysis in the blood sample before assay.[5]

Thus the high incidence of low serum glucose concentrations in the babies studied by Sexson[1] may simply be because 72% of the babies studied had one or more of the recognised risk factors for hypoglycaemia.

The concern regarding the definition of hypoglycaemia arises from the established risk of neurological damage after repeated and prolonged episodes of low circulating glucose concentrations.[5] This concern needs to be balanced by the need to avoid the unnecessary treatment and investigation of otherwise healthy babies. We suggest a more rational approach to the definition of hypoglycaemia would be to derive a functional definition based on a correlation between objective measurements of neurophysiological function and blood glucose concentrations. Indeed, such studies may show that the 'safe' blood glucose concentration may be different in varying clinical situations—for example, during hypoxia, polycythaemia, or convulsions—rather than being dependent upon the babies' gestational and postnatal age and birth weight. Further research is needed urgently to resolve the dilemma over the definition of hypoglycaemia in the neonatal period.

We would like to thank all the paediatricians who completed and returned the questionnaires. Support from the Newcastle Health Authority is acknowledged THHG Koh is an MRC training fellow

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Accepted 3 May 1988

Transient neonatal galactosaemia

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SUMMARY A 4 week old infant who failed to thrive was found to have galactose in his urine. Plasma galactose concentration was grossly raised (4·48 mmol/l; reference range <0·24 mmol/l) but red cell transferase and epimerase activities were normal. He improved when dietary lactose was excluded. Clinical and biochemical tolerance to galactose was evident by 7 months of age.

Galactosaemia is a rare disorder (1/72 000 in the United Kingdom)[1] which presents classically with vomiting, diarrhoea, listlessness, and failure to thrive. Symptoms often start within the first week of life. Persistent jaundice may suggest the diagnosis and by two weeks hepatosplenomegaly and lenticular opacifications are easily detectable. Biochemical galactose intolerance may also occur secondarily to severe disease of the liver parenchyma.[2] We report an infant with galactose intolerance who failed to thrive yet had normal galactose-1-phosphate uridyl transferase (G_1PT) activity and evidence of only mild hepatic dysfunction.

Case report

A boy, the first child of unrelated parents, was born weighing 2380 g after an induced delivery at 36 weeks' gestation for maternal pre-eclampsia. There was no significant family history and the pregnancy was otherwise uneventful. The baby was initially breast fed but at 20 hours of age he was transferred to the special care baby unit because of poor feeding. He was found to be hypothermic (34·6°C) and hypoglycaemic (blood glucose concentration <1 mmol/l). At 4 days of age he became jaundiced (maximum serum bilirubin concentration 265 μmol/l on day 5) but this settled and he was discharged at 9 days. Over the next three weeks he became increasingly irritable, fed poorly with frequent possetting, and needed supplementation with formula milk. He had not regained his birth weight. Physical examination showed no abnormality except for mild generalised hypotonia.

A urine sample screened for metabolic abnormalities at 1 month of age contained reducing substances identified as galactose at a concentration of 11 mmol/l. Investigations that gave normal results at this time were full blood count, electrolytes, calcium, random blood glucose, thyroid function tests, a screen for toxoplasma, other viruses, rubella, cytomegalovirus, and herpes virus, α_1 antitrypsin phenotype, and hepatitis B surface antigen. Liver function tests at 1 month of age were abnormal (reference ranges given in brackets): bilirubin 64 µmol/l (<20), direct bilirubin 12 µmol/l (<10), alkaline phosphatase 682 IU/l (135–550), total protein 38 g/l (55–75), and albumin 21 g/l (30–50); aminotransferase activities were normal. Blood and urine amino acid and urine organic acid concentrations were normal. The screening test for galactosaemia was normal as were the activities of G_1PT and uridine diphosphate galactose epimerase. The plasma galactose concentration at this time was 4·48 mmol/l (normal <0·24 mmol/l). Between 2 and 3 months of age there was a peak alkaline phosphatase activity of 1000 IU/l with a γ-glutamyltransferase of 203 IU/l (<45) and raised transaminases (aspartate aminotransferase 79 IU/l (<40), alanine aminotransferase 58 IU/l (<30)). Subsequently alkaline phosphatase and plasma protein concentrations became normal but the transaminase activities remained borderline raised. No cataracts were found on ophthalmological examination. At the age of 2 months the baby required a blood transfusion for anaemia (haemoglobin concentration 72 g/l, reticulocytes 5·9%).

It was felt that, in view of the symptoms and high plasma galactose concentrations, galactose should be excluded from the diet and a lactose free soy formula milk was prescribed (Formula S, Cow and Gate). Immediately his mother noticed a change in his behaviour, the infant becoming more placid and content. He gained weight rapidly and his muscle tone returned to normal. Plasma galactose concentrations fell to 0·03 mmol/l and galactose disappeared from the urine. The baby was challenged with galactose at an age of 3 months (6·5 g orally) resulting in a peak plasma galactose concentration of 2·56 mmol/l, which showed a continuing galactose intolerance. Erythrocyte galactose-1-phosphate concentrations, however, responded normally confirming that there was no impairment of the transferase pathway.

At 7 months of age his transaminase activities remained borderline raised but other liver function tests were normal and his galactose tolerance was investigated with an intravenous galactose load.[3] Plasma galactose concentrations during the test decreased with a normal half life of 5 minutes (see figure). A supervised reintroduction of cows' milk was performed at 10 months without sequelae. One month later he was found to be thriving on a normal diet. His development is normal.

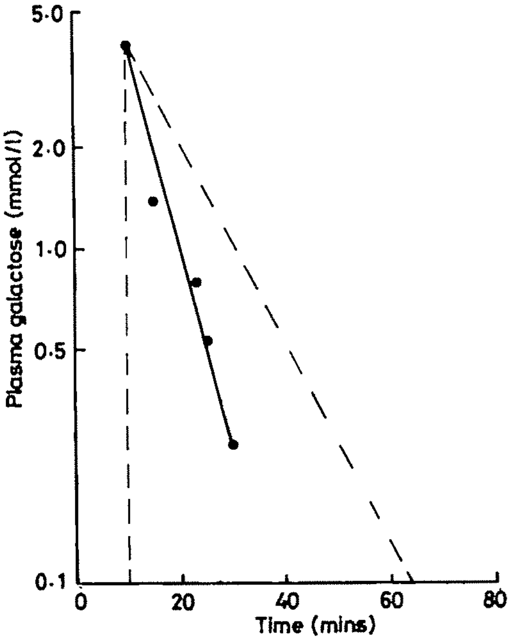

Figure *Semilogarithmic plot of plasma galactose concentrations after a bolus injection of D(+) galactose 350 mg/kg body weight Dashed lines indicate the limit of the normal range of half lives for this age (up to 10 minutes[3])*

Discussion

There have been many recorded variants of galactosaemia but this child did not appear to fall into any of these categories.[4] Classical galactosaemia due to transferase deficiency was excluded by the normal activity of the enzyme. There was no negro blood in the family, a factor previously noted in children with transferase variants. All children with galactokinase deficiency have had cataracts, which this child did not, are asymptomatic at birth, and grow normally. The possibility of a deficiency of the epimerase type was considered but was excluded by enzyme assay. Kelly described suggestive symptoms or biochemical evidence of galactose intolerance in six of seven infants with the Duarte/classical galactosaemic genetic compound.[5] Although at least two of these infants subsequently became galactose tolerant by 15 months, most were asymptomatic and blood galactose concentrations were substantially below those reported here. All seven had abnormal transferase activity.

It is possible that there had been transient liver damage in this child at or before delivery resulting in an inability to metabolise galactose. Galactose intolerance in association with liver disease is well known and galactose challenge has been used as a dynamic test of liver function.[3] Pronounced galactose intolerance, however, is usually associated with severe liver disease.[2] Hepatosplenomegaly was not noted in this infant and biochemical evidence was limited to moderate transient abnormalities of alkaline phosphatase, γ-glutamyltransferase, albumin, and a persisting borderline rise of transaminase activities. Early jaundice and anaemia are both features of galactosaemia; however, the jaundice was transient, and both prematurity and frequent blood sampling may have been contributory factors.

This child appears to be unusual in the degree of his intolerance to galactose in the absence of any detectable defect in galactose pathways and in the presence of only minimal biochemical evidence of liver disease This intolerance appeared to be physiological as well as biochemical as the child's health improved promptly when he was given a galactose free diet. It appears unlikely that the biochemical and clinical improvements were unrelated. It is important that children with galactose intolerance other than that due to inherited enzyme deficiencies be challenged with galactose at intervals so that they can return to normal feeds as soon as they are able to tolerate them.

Quantitative assays of erythrocyte enzymes and of galactose-1-phosphate were performed by the department of clinical chemistry, Southmead Hospital, Bristol

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Oral vancomycin in prevention of necrotising enterocolitis

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SUMMARY Eighty four very low birthweight babies (considered high risk for developing necrotising enterocolitis) were given vancomycin orally for 48 hours before introduction of oral feeds; one developed necrotising enterocolitis One hundred and twenty very low birthweight babies (not considered such high risk) were fed without first receiving vancomycin; 17 developed necrotising enterocolitis. Although this was not a randomised control trial, results indicate a role for vancomycin in prophylaxis of necrotising enterocolitis.

The exact sequence of pathological events in necrotising enterocolitis has not been established, although there is general agreement that prematurity and neonatal illness predispose to it, and that invasion of the bowel wall by bacteria is the ultimate and most serious aspect of the pathological process. It is also widely accepted that necrotising enterocolitis rarely develops in babies who have not received enteral feeds and indeed often manifests soon after feeds have been introduced. It could be that gut bacteria require food substrate in order to multiply sufficiently to invade the susceptible bowel wall. If this hypothesis is correct, then reducing the bacterial population in the bowel, particularly the gas producing anaerobes, before introducing milk feeds could reduce the incidence of necrotising enterocolitis.

According to this line of reasoning it has been our policy, during the past three years, to treat very low birthweight babies who have had prolonged intensive care, and are therefore at high risk of developing necrotising enterocolitis, with oral vancomycin for 48 hours before starting milk feeds. Vancomycin was chosen because of its activity against clostridial species and other anaerobes, and because it does not completely sterilise the bowel, which could promote colonisation by unwanted pathogens. Furthermore, vancomycin is poorly absorbed and so a high drug concentration can be achieved in the gut with minimal risk of systemic toxicity.

This paper presents our experience with necrotising enterocolitis during the three years that we have used vancomycin prophylaxis.

Patients and methods

During the three consecutive years from January 1984 to December 1986, 204 very low birthweight babies were admitted to our neonatal unit.

The decision to use vancomycin in a particular case was made neither by defined criteria nor by randomisation, but rather by a consensus of clinical opinion that the baby was at risk of necrotising enterocolitis because of the severity of previous illness. Accordingly, 84 babies were given oral vancomycin for 48 hours before the start of enteral feeding and 120 babies did not receive the drug. Vancomycin was given in doses of 15 mg/kg eight hourly, for six doses.

Milk feeds were given as intermittent boluses, starting at 1 ml hourly and gradually increasing according to tolerance. Babies were fed human milk whenever possible but a number of commercial formulas were also used.

With regard to outcome, babies were diagnosed as having necrotising entercolitis if they had an illness characterised by abdominal distension, blood in the stools, and intramural gas on abdominal radiography.

We used unpaired *t* tests for analysis of parametric data, and the Mann-Whitney U test for non-parametric data.

Results

A total of 28 babies in the group who did not receive vancomycin died within the first 5 days of life before oral feeds were considered. None of them had necrotising enterocolitis. They have been excluded from the analysis, leaving 92 babies in this group.

Table 1 compares the characteristics and occurrence of necrotising enterocolitis between the groups receiving or not receiving vancomycin treatment. The babies selected to receive vancomycin were, as expected, significantly less mature, smaller, in poorer condition at birth, ventilated for longer, and were more likely to have had an umbilical catheter. They were also significantly older when enteral feeds were first introduced This is to be expected among a selected high risk group as it is the policy of the unit to delay enteral feeds until babies are free of major respiratory symptoms. A standard parenteral nutrition regime was used until then.

Eighteen cases of definite necrotising enterocolitis were seen during the study period. Seventeen infants were in the group not receiving vancomycin and only one infant was in the group receiving vancomycin (table 2). This difference was significant ($\chi^2=12\cdot47$, $p<0\cdot001$). In the group not receiving vancomycin, three babies died of necrotising enterocolitis. The baby in the group receiving vancomycin underwent surgery but survived. The cases of necrotising enterocolitis were evenly spread throughout the study period and there was no outbreak noted. There was no association between the occurrence of necrotising enterocolitis and the type of milk fed.

Certain clinical features of the 17 babies in the group not receiving vancomycin who developed necrotising enterocolitis were significantly different compared with the 75 babies not receiving vancomycin who did not suffer necrotising enterocolitis (table 2). Those who suffered necrotising enterocolitis had clinical features that were in fact more similar to the group receiving vancomycin, differing significantly only in respect of the later age at which the vancomycin group were first enterally fed.

Discussion

Considering that infection is undoubtedly an impor-

Table 1 *Comparison of characteristics between the two groups.* Results are mean (SD) and range*

	Group receiving vancomycin		*Group not receiving vancomycin*	
Gestation (weeks)	28·5 (2·4)	24–34	29·8 (2·5)	25–35
Birth weight (g)	1100 (251)	630–1500	1204 (205)	625–1500
Duration of ventilation (days)	24·5 (26·5)	0–114	5·7 (10·4)	0–63
Apgar score at 1 minute	5	0–10	6	1–10
Apgar score at 5 minutes	7	1–10	9	4–10
Age when enteral feeds introduced (days)	24·7 (19·8)	2–97	6·8 (6·2)	1–40
Incidence of umbilical artery catheterisation (%)		82		66
Incidence of necrotising enterocolitis	1 case		17 cases	
Age at onset of necrotising enterocolitis (days)	55		19·8	(3–37)

*There was a significant difference (at the $p<0\cdot02$ level) between the treated and non-treated babies for all the characteristics shown in this table

Table 2 *Comparison between babies with and without necrotising enterocolitis in the group not receiving vancomycin.* Results are mean (SD) and range*

	Babies with necrotising enterocolitis		*Babies without necrotising enterocolitis*	
Gestation (weeks)	28·4 (1·8)	26–32	30·2 (2·6)	25–35
Birth weight (g)	1114 (193)	860–1400	1269 (198)	625–1500
Duration of ventilation (days)	13·9 (17·5)	0–63	3·9 (7·1)	0–54
Apgar score at 1 minute	5	1–8	6	1–10
Apgar score at 5 minutes	8	7–10	9	4–10
Age when enteral feeds introduced (days)	10 (5·3)	2–21	6·2 (6·2)	1–40
Incidence of umbilical artery catheterisation (%)		88		61

*There was a significant difference (at the $p<0·03$ level) between the babies who developed necrotising enterocolitis and those who did not for all the characteristics shown in this table

tant aetiological factor in necrotising enterocolitis, it is surprising that there have been only four controlled trials of antibacterial prophylaxis.[1-4] Two of these trials used kanamycin, one showing a significant benefit[1] and the other not,[2] and two used gentamicin, both purporting to show benefit. In addition there is the uncontrolled observation suggesting that oral vancomycin might have helped to terminate an epidemic of necrotising enterocolitis.[5] The question of whether necrotising enterocolitis can be prevented by antibacterial agents therefore deserves further examination.

The experience that we report in this paper does not derive from an attempt to conduct an experiment, but is rather a retrospective review of the effects of a change in clinical practice As no attempt at randomisation was made there was inevitably bias in the allocation to treatment or non-treatment groups. Indeed there was a deliberate effort to treat with vancomycin those babies judged most susceptible to necrotising enterocolitis according to the generally accepted risk criteria, and in this sense selection bias provides an even more rigorous test of the prophylactic value of vancomycin in necrotising enterocolitis. Interestingly, the 17 babies in the group not receiving vancomycin who developed necrotising enterocolitis are not typical of the non-treatment group as a whole. In terms of the putative risk factors—namely, shorter gestation, lower birth weight, poorer condition at birth, and more prolonged ventilation—they were appreciably more at risk than the remainder of the group not receiving vancomycin. In a formal study, the 17 babies in question might have been identified as 'at risk' and therefore treated. Decision making in routine clinical practice is, however rarely as rigorous as it might be.

While selection bias undoubtedly strengthens the conclusion that something occurring to the group receiving vancomycin resulted in a significant reduction in the expected incidence of necrotising enterocolitis, it prevents us from concluding with certainty that it was vancomycin. A possible alternative explanation is the difference between the two groups in the age at which feeds were introduced.[6] The group receiving vancomycin were first fed at a mean of 24·7 days of age and the group not receiving vancomycin at a mean of 6·8 days. This difference reflects our policy of delaying the introduction of enteral feeding until babies are out of intensive care. It is important to note, however, that the 17 babies who developed necrotising enterocolitis were first fed at a mean age of 10 days which is significantly *later* than the rest of the non-treatment group who escaped necrotising enterocolitis. Only a prospective randomised trial can decide whether it is the use of vancomycin or the delaying of enteral feeds (or indeed some other factor) that was responsible for preventing necrotising enterocolitis in our treatment group.

An inevitable worry associated with the widespread prophylactic use of any antibiotic is that of inducing resistance in bacteria. Vancomycin has a remarkable reputation for not doing so, and it has been in use for a long time. Further investigation of this would be desirable if vancomycin prophylaxis in the very low birthweight baby was to be generally adopted.

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Accepted 27 June 1988

Congenital syphilis in the newborn

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SUMMARY We studied 53 newborn babies with congenital syphilis. The common clinical features seen were low birth weight, hepatosplenomegaly, anaemia, jaundice, and symmetrical superficial desquamation of the skin affecting palms and soles. The presence of these clinical signs is highly suggestive of early congenital syphilis. Hydrops fetalis without rhesus or ABO isoimmunisation should always arouse the suspicion of congenital syphilis.

Sexually transmitted diseases continue to be a serious public health problem all over the world. In recent years an increase in the incidence of acquired and congenital syphilis has been reported from both developed and developing countries.[1] The present study, which emphasises the neonatal aspects of this disease, was undertaken to document the clinical range of congenital syphilis in the neonatal period, identify common clinical features of the disease in this age group, and assess the immediate prognosis of the disease in the neonatal period.

Patients and methods

Newborn babies included in the study were born in the greater Harare area and admitted to the neonatal unit, Harare Central Hospital, which is the referral centre for all high risk newborn babies in the city of Harare, Zimbabwe. The total number of newborns admitted to the neonatal unit during the study period, 1 January to 31 December 1986, was 5287.

The diagnosis of early congenital syphilis was based on positive serology for syphilis in mother or infant, or both, in the presence of two or more clinical signs suggestive of early congenital syphilis.[2] The clinical signs regarded as suggestive of early congenital syphilis were as follows: (a) haematological manifestations—that is, anaemia, thrombocytopenia; (b) hepatomegaly or hepatosplenomegaly; (c) jaundice; (d) mucocutaneous lesions—for example, snuffles, condylomata lata; skin rash, peeling skin of palms and soles, etc; (e) nonimmune hydrops; (f) Parrot's pseudoparalysis; and (g) radiological appearance in the long bones suggestive of congenital syphilis.

The serological tests employed for establishing the diagnosis of congenital syphilis were the rapid plasma reagin test and *Treponema pallidum* haemagglutination assay. A total of 53 newborn babies fulfilled the diagnostic criteria laid down above and were included in the study.

Results

The frequency of clinical features at presentation is shown in the table. Hepatomegaly or hepatosplenomegaly of 2 cm to 6 cm was present in 28 (53%) and 26 (49%) patients respectively. Clinical jaundice was noted in 25 infants (47%). Unconjugated hyperbilirubinaemia was much more common than

Table *Frequency of clinical features in 53 newborn babies with congenital syphilis*

Clinical feature	*No (%)*
Low birth weight	41 (77)
Hepatomegaly	28 (53)
Splenomegaly	27 (51)
Hepatosplenomegaly	26 (49)
Anaemia*	16 (50)
Thrombocytopenia	12 (38)
Jaundice	25 (47)
Skin lesions	20 (38)
Respiratory distress	10 (19)
Hydrops fetalis	3 (6)
Snuffles	2 (4)
Pseudoparalysis	2 (4)

*Haemoglobin concentrations and platelet counts were available in 32 babies only, therefore percentages are from a total number of 32 conjugated hyperbilirubinaemia. Bilateral symmetrical desquamation of the skin of the upper and lower extremities, especially affecting the medial part of thighs, palms, and soles, was the commonest skin lesion observed. Vesiculobullous lesions, which when they ruptured left behind raw denuded oozing areas, were present in a few cases only.

In all the 10 infants who developed respiratory distress, the onset was within the first 24 hours of life. The clinical course was compatible with the diagnosis of hyaline membrane disease in four, neonatal sepsis in three, and transient tachypnoea of the newborn in two. One patient remained tachypnoeic beyond the neonatal period and was still tachypnoeic at the age of 2 months and could have had syphilitic pneumonitis.

Haemoglobin concentrations and platelet counts were available on 32 (60%) newborns only. Anaemia (haemoglobin concentration <135 g/l) was present in 16 (50%) cases; the lowest haemoglobin concentration recorded was 67 g/l. Thrombocytopenia (platelet count $<150\times10^9$/l) was present in 12 cases (37%). Bleeding from injection sites was noted in one infant who had a platelet count of $55\cdot$[illegible]$\times10^9$/l).

The case fatality rate in the present study was 13% (seven out of 53). All these seven infants were low birthweight neonates. Nonimmune hydrops was present in three. Six of the seven deaths (86%) were early neonatal deaths, and one (14%) was a late neonatal death. In addition to the stigmata of congenital syphilis, mild to moderate respiratory distress was present in five cases, apnoeic attacks in one, meconium aspiration and birth asphyxia in one each. These conditions may have also contributed towards the death in these seven infants.

Discussion

The classical clinical manifestations of early congenital syphilis are rare in the neonatal period with most becoming symptomatic within first 3 months of life.[1] Disease can be identified in the newborn, however, if a high degree of suspicion is exercised.[3 4] Low birth weight, hepatosplenomegaly, anaemia, jaundice, and superficial desquamation of palms and soles were the most frequent clinical signs observed in the present study. The incidence of hepatosplenomegaly among our patients was much lower when compared with the incidence of 90–100% reported by the other authors.[4 5] Neonatal jaundice was a common clinical mode of presentation and was present in 47% of the newborns. Hira *et al* showed that 44% of newborn babies with early congenital syphilis were jaundiced when compared with 3% of infants in the postneonatal period.[3] A previous study by one of us (VC) in Zambia showed that jaundice was present in 77% of the newborn babies with syphilis while only 6% of infants with syphilis in the postneonatal period had jaundice.[2]

The characteristic bilateral, symmetrical, hypopigmented skin lesions affecting buttocks, upper and lower extremities, and napkin area were relatively infrequent in the newborn.[2 3] An erythematous shiny appearance of the soles and palms with superficial peeling of the skin was the commonest cutaneous manifestation observed and was very helpful in early diagnosis. Other mucocutaneous manifestations like snuffles (4%) and condylomata lata are also infrequent in the neonatal period.[2 3] Pseudoparalysis is rare in the neonatal period and was observed in only two cases (4%).

The role of congenital syphilis in the pathogenesis of intrauterine growth retardation is controversial. In the present study 77% of the newborn babies were of low birth weight, which is similar to the incidence of 76% and 81% reported by Hira *et al*[3] and Tan [5] Others, however, have found no significant difference in the incidence of low birth weight among the newborn babies of seropositive and seronegative mothers.[6]

The high mortality rate in the neonatal period despite adequate treatment is probably due to irreversible damage resulting from overwhelming spirochaetaemia. If the infant survives the neonatal period the prognosis with treatment is good.[3] The overall case fatality rate in the present study was 13%, which is much lower than the case fatality rates reported by other authors.[4 5] The presence of nonimmune hydrops carries a poor prognosis.[5] All the three patients with hydrops died.

The authors would like to thank the permanent secretary, Ministry of Health and the medical superintendent, Harare Central Hospital, for their permission to publish this paper, Mrs Mafuma and Mr Mudzingwa for helping with the serology, and Miss B Ncube for the secretarial help

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Accepted 26 June 1988

Arterialisation of transcutaneous oxygen and carbon dioxide

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SUMMARY We compared previously calculated global correction factors for oxygen and carbon dioxide arterial/transcutaneous ratios with individual in vivo calibrations from the first arterial sample In infants beyond the neonatal period and older children in vivo calibration confers little benefit over the use of a global calibration correction factor for transcutaneous carbon dioxide, and may reduce the precision with which arterial oxygen can be estimated from transcutaneous oxygen.

Transcutaneous oxygen and carbon dioxide provide a convenient, non-invasive method for continuous respiratory monitoring. Transcutaneous oxygen underestimates arterial oxygen because of the skin diffusion barrier to oxygen while transcutaneous carbon dioxide overestimates arterial carbon dioxide because of carbon dioxide production by the skin. These problems may be overcome by allowing for carbon dioxide production by the skin and the oxygen diffusion barrier by using a global correction at calibration.

An alternative approach is to correct transcutaneous readings using arterial blood gas samples. This in vivo calibration assumes that arterial/transcutaneous relationships remain relatively constant in any one individual. We have previously found in children and infants beyond the neonatal period a mean arterial/transcutaneous oxygen ratio of 1·22[1] and an arterial/transcutaneous carbon dioxide ratio of 0·714.[2] We therefore compared in vivo calibration with these global correction calibrations in children undergoing intensive care.

Patients and methods

Data were available from 38 children (17 girls and 21 boys), who had indwelling arterial lines as part of their routine management. Median age was 1·3 (range 0·01 to 11·75 years). Three subjects were neonates all of whom were full term, and all children were haemodynamically stable throughout the study period.

Transcutaneous measurements were made using individual oxygen and carbon dioxide electrodes (Kontron 232 and 230) heated to 44°C. Oxygen electrodes were calibrated in room air, and carbon dioxide electrodes against 5% and 10% carbon dioxide. No corrections were made for varying barometric pressure (assumed to be 101·3 kPa) or for ambient humidity. The electrodes were applied to the upper anterior chest wall, and 30 minutes were allowed for equilibration.

Arterial blood samples were then taken at hourly intervals for four hours, at times when transcutaneous readings had been stable for at least two minutes. Blood gas measurements were performed using a Radiometer ABL2 blood gas analyser, which was calibrated twice daily with reference solutions and once weekly with tonometered blood.

GLOBAL CORRECTION CALIBRATION

All transcutaneous oxygen values were multiplied by 1·22 (equivalent to calibrating the electrode to read 25·6 kPa in air),[1] and all transcutaneous carbon dioxide values were multiplied by 0·714 (equivalent to calibrating the electrode to read 7·07 kPa in 10% carbon dioxide).[2]

IN VIVO CALIBRATION

At the first hourly blood sample, the arterial/transcutaneous ratios for oxygen and carbon dioxide were calculated for each patient. These individual ratios were then used as correction factors for all subsequent transcutaneous oxygen and transcutaneous carbon dioxide measurements within each patient.

Global correction and in vivo corrected transcutaneous values were subtracted from subsequent simultaneous arterial values to give the mean errors of prediction of arterial oxygen and arterial carbon dioxide together with their respective confidence intervals.[3]

Results

(1) OXYGEN MEASUREMENTS

Arterial oxygen ranged from 4·87 kPa to 27·47 kPa. One hour after in vivo calibration, the confidence intervals of the prediction error for arterial oxygen were slightly narrower than those found after global correction. At three hours after in vivo calibration (four hours after equilibration) in vivo corrected values were less precise with an increased prediction error (table 1).

Arterial/uncorrected transcutaneous oxygen ratios

Table 1 *Prediction of arterial oxygen*

	Mean (SD) error (kPa)	*95% Confidence interval (kPa)*	*No of observations*
One hour global	0·57 (1·28)	−2·11 to 3·25	38
One hour in vivo	0·55 (1·29)	−1·93 to 3·03	38
Three hour global	0·39 (1·85)	−3·43 to 4·20	28
Three hour in vivo	0·49 (2·36)	−4·37 to 5·35	28

Table 2 *Prediction of arterial carbon dioxide*

	Mean (SD) error (kPa)	*95% Confidence interval (kPa)*	*No of observations*
One hour global	0·09 (0·55)	−1·25 to 1·43	25
One hour in vivo	−0·11 (0·45)	−1·01 to 0·79	25
Three hour global	0·03 (0·78)	−1·52 to 1·57	18
Three hour in vivo	−0·19 (0·53)	−1·49 to 1·13	18

changed within individuals with time, the mean change from hour one, to hour four was small—1·23 to 1·20—and the respective SDs were 0·15 and 0·20. Arterial/uncorrected transcutaneous ratios had changed by more than 15% in five out of 38 studies at two hours, in seven out of 38 at three hours, and in 11 out of 28 at four hours. Mean arterial/uncorrected transcutaneous oxygen and its variability were independent of arterial oxygen.

(2) CARBON DIOXIDE MEASUREMENTS

The number of observations for carbon dioxide were less than for oxygen (25 compared with 38) with 18 data points available at four hours, and arterial carbon dioxide ranged from 2·6 kPa to 11·73 kPa. In vivo calibration produced a small improvement in the precision with which arterial carbon dioxide could be estimated (table 2).

Mean arterial/uncorrected transcutaneous carbon dioxide rose from 0·689 at one hour to 0·727 at four hours and the respective SDs rose from 0·062 to 0·135. The proportion of children in whom arterial/uncorrected transcutaneous carbon dioxide changed by more than 15% was lower than for oxygen: three out of 25 at two and three hours and four out of 18 at four hours.

Discussion

In vivo calibration does not appear to confer any clinically important benefit over global correction factors applied at calibration. Indeed, in the case of transcutaneous oxygen, there is a trend towards a reduction in predictive power of arterial oxygen after in vivo calibration (table 1).

Within an individual, arterial/uncorrected transcutaneous oxygen and arterial/uncorrected transcutaneous carbon dioxide change with time and from our data these changes appear to be more pronounced for oxygen than for carbon dioxide. For those children with unstable arterial/transcutaneous ratios, in vivo calibration gives a false sense of security and may result in errors that are unknown and unpredictable. Use of global calibration correction factors derived from the appropriate population results in transcutaneous values in which the errors of estimation of arterial oxygen and carbon dioxide are known. In fullterm infants and older children increasing age does not appear to affect arterial/transcutaneous relationships for oxygen or carbon dioxide.[1 2 4] In premature infants, however, this is not the case,[5 6] and in them it may be more appropriate to use intermittent in vivo calibration.

The confidence interval of ±4–5 kPa 4·5 hours after electrode placement for transcutaneous oxygen is large but is certainly narrow enough to detect clinically important changes in oxygenation. These data, however, yet again emphasise the importance of regular arterial sampling to confirm trends displayed on transcutaneous machines.

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Accepted 10 May 1988

Diabetic complications in a prepubertal adolescent

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SUMMARY A 13 year old boy, with a five year history of diabetes mellitus, developed a severe neuropathy and a transient deterioration of a background retinopathy after initiation of improved glycaemic control. This followed a long period of extremely poor metabolic control, with growth retardation and weight loss.

Diabetic complications are related to the duration of diabetes and are rarely seen in children before puberty. In this paper, we report a prepubertal boy with a five year history of insulin dependent diabetes with severe neuropathy and transient deterioration of retinopathy after initiation of improved metabolic control.

Case report

The boy had insulin dependent diabetes mellitus from the age of 8½ years. For the next few years his diabetes was neglected by his foster parents and, after a remission period of less than one year, he had extremely poor metabolic control with a glycated haemoglobin (HbA_1) concentration of 16·7–20·2% (normal, <7·8%). At the age of 13 he started to lose weight and had some pain in both legs. At this stage, he was removed from his foster home. He was admitted to hospital and given a new insulin regimen with a mixture of regular and isophane insulin before breakfast and dinner with a total insulin requirement of 2·1 U/kg. The insulin regimen was later changed into three injections daily and the insulin requirement reduced to 1·6 U/kg. After a short while his metabolic control was greatly improved. A few weeks later he experienced increasing pain in both lower legs, difficulty in walking, loss of appetite, and depression.

He was admitted to our hospital about two and a half months after he had started his new insulin regimen at the local hospital. On admission, he was 13½ years old, his height was 141 cm (2 cm less than −2 SD), weight 24·3 kg (−2 SD related to height), and bone age 11 years. For comparison, when he was 10½ years old, his height was 138·5 cm (−1 SD) and weight 30·8 kg. Therefore in the three proceeding years his growth had been only about 1 cm per year, and his weight had declined by 6·5 kg.

Physical examination showed no sign of puberty (Tanner stage 1). In both lower legs he had signs and symptoms of polyneuropathy with muscular atrophy, dysaesthesia, and burning pain. Electromyelography and nerve conduction velocity showed findings consistent with a moderate general motor and sensory polyneuropathy. There were reduced motor nerve conduction velocities and the sensory fibres were affected with increased threshold for sensory stimulation. During his hospital stay he had persistent sinus tachycardia, but an autonomic test using R-R interval after standing up was normal. There was background retinopathy bilaterally with soft exudates and some haemorrhages, together with slight opacities in both lenses. On admission his HbA_{1c} concentration was 7·5% (normal range, 4·3–6·1%), and he had borderline values when testing for microalbuminuria.

During the next few months the pain in his legs slowly improved. After another few months he could no longer walk and was dependent on a wheelchair. Eye control after five months showed a few microaneurysms and, after one year, an almost total reversal of the retinopathy. After one year, there were still reduced motor nerve conduction velocities, but with slight improvement of these in the upper extremities. After intensive physiotherapy for one and a half years, he is able to walk with one crutch.

Discussion

Major diabetic complications are rarely seen in prepubertal children. The prevalence of early diabetic retinopathy in children and adolescents with the same duration of diabetes and a similar level of glycaemic control is appreciably greater in late pubertal subjects as compared with prepubertal subjects.[1] For children less than 15 years of age with less than a five year duration of diabetes, retinal lesions are rare. The prevalence of microalbuminuria, which is considered to be a predictor of diabetic nephropathy, is very low before 13–15 years of age. Several studies have suggested that there is a connection between puberty, sex hormones, and development of microvascular disease.

Clinical signs of diabetic neuropathy are very uncommon in children. Electroneurophysiological studies, however, have shown subclinical abnormalities with decreased nerve conduction velocities even in prepubertal diabetic children.[2]

Daneman *et al* reported four similar cases with Mauriac syndrome with progressive retinopathy after improvement of diabetic control.[3] Another case was reported by Lawrence *et al* with rapidly progressive retinopathy after improved metabolic control.[4] Transient deterioration of retinopathy has also been seen in randomised trials with continuous subcutaneous insulin infusion compared with conventional treatment after rapid change of blood glucose control.[5] The retinal changes seen in our patient are similar to those seen in some of the patients on continuous subcutaneous insulin infusion. It is likely that the mechanisms for the transient deterioration of the retinopathy after improved glycaemic control are the same both in the poorly controlled diabetic children and the patients on continuous subcutaneous insulin infusion.

None of the patients reported by Daneman and Lawrence had clinical neuropathy. Diabetic neuropathy is rarely reported within the first five years of type 1 diabetes, and the prevalence is related to the duration of diabetes. Hyperglycaemia seems to be an important aetiological factor in the pathogenesis of diabetic neuropathy. Worsening of neuropathy after the initiation of improved blood glucose control, as seen in our case, has been reported. Most of these publications are of neuropathy precipitated by the initiation of treatment with insulin or other hypoglycaemic agents. Dandona *et al* reported a case of an 18 year old girl with 'brittle' diabetes who developed painful neuropathy a few weeks after starting treatment with continuous subcutaneous insulin infusion.[6] It has been suggested that the symptoms of pain seen after improved glycaemic control may reflect repair and regeneration of damaged nerve fibres.

Diabetic complications in prepubertal children seem to be related to extremely poor metabolic control and unfavourable psychosocial factors. We recommend that special care should be taken when initiating improved diabetic treatment in such children with very poor glycaemic control.

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Accepted 19 July 1988

Archives of Disease in Childhood, 1988, **63,** 1399–1404

Personal practice

Management of congenital adrenal hyperplasia

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Congenital adrenal hyperplasia is the commonest adrenal disorder in infancy and childhood and results from a deficiency in the activity of one of the five enzymes required for cortisol biosynthesis.[1] More than 90% of cases are due to a deficiency of 21-hydroxylase enzymes required for the conversion of 17OH-progesterone to 11-deoxycortisol and of progesterone to 11-deoxycorticosterone. The inheritance is autosomal recessive and the monogenic trait is closely linked to the HLA locus on chromosome 6.[2] A further 5% of cases are associated with a deficiency of the 11β-hydroxylase enzyme involved in the terminal steps of cortisol and aldosterone biosynthesis. The clinical hallmark of both enzyme defects is virilisation consequent upon increased adrenocorticotrophic hormone secretion causing excess adrenal androgen production. The remaining enzyme defects causing congenital adrenal hyperplasia are very rare and their management is not discussed.

Clinical presentation

Fetal adrenal steroidogenesis is established in early gestation so that a female fetus with congenital adrenal hyperplasia invariably has virilised external genitalia at birth. The degree of virilisation can range from mild isolated clitoromegaly or partial labial fusion to complete fusion of the labioscrotal folds ('scrotalised' labia) and pronounced clitoromegaly with a phallic urethra. The latter variant may masquerade as a cryptorchid 'male' with or without hypospadias. The consequences of inappropriate gender assignment can be tragic when the true sex is realised in later life.[3] The clitoris and labia minora may be sufficiently prominent in an otherwise normal preterm female infant to raise a suspicion of partial virilisation of the genitalia Sometimes an affected girl does not show signs of virilisation at birth. This late onset variant of congenital adrenal hyperplasia usually presents with the onset of early pubic or labial hair growth and accelerated linear growth. A boy with congenital adrenal hyperplasia rarely has signs of virilisation at birth despite plasma testosterone concentrations which are often within the normal adult male range Increased pigmentation of the scrotal skin may sometimes be a clue to the diagnosis. Typically the affected boy is recognised as the result of a salt losing crisis, which presents during the second or third week of life. A mistaken diagnosis of pyloric stenosis has been made occasionally but the electrolyte pattern should distinguish the two disorders. Many families with patients who have congenital adrenal hyperplasia report a history of previous unexplained male infant deaths.[4] It is my impression that with the increased awareness of the disorder by paediatricians, and the availability of rapid diagnostic tests, cases of salt losing congenital adrenal hyperplasia are now rarely missed in this country.

About one third of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency are non-salt losers. Males with this form of congenital adrenal hyperplasia are not clinically detected at birth and show signs of virilisation in late infancy and childhood. The signs include growth of the penis and pubic hair, increased muscle bulk, and rapid linear growth. The testes remain prepubertal in size. This is an important clinical sign to indicate that the increased androgen production arises from a peripheral (adrenal) source which is independent of central gonadotrophin stimulation. It is now recognised that there is a wide range of clinical manifestations of 21-hydroxylase deficiency. The examples are summarised in table 1. A simple classification into classical and non-classical forms of congenital adrenal hyperplasia has been proposed based on phenotype (symptomatic or asymptomatic).[5] In classical congenital adrenal hyperplasia, there is prenatal virilisation, which may also be accompanied by early postnatal salt wasting. Non-classical congenital adrenal hyperplasia includes patients with postnatal or late onset virilisation or those who are asymptomatic but show abnormalities on biochemical testing. These are referred to as cryptic cases in table 1 and are usually identified when relatives of an index case

Table 1 *Clinical manifestations of 21-hydroxylase deficiency*

Newborn	*Later life*
Ambiguous genitalia:	Pseudoprecocious puberty
Complete	Isolated pubarche
Isolated clitoromegaly	Isolated clitoromegaly
Isolated labial fusion	Rapid growth
	Hirsutism
Cryptorchid, hypospadic 'male'	Menstrual disorders
	Infertility
Salt wasting	Cryptic cases

with classical congenital adrenal hyperplasia are investigated.

Girls with congenital adrenal hyperplasia due to 11β-hydroxylase deficiency are also virilised at birth and the degree may be more severe than in the 21-hydroxylase defect. Salt wasting is not a feature of untreated 11β-hydroxylase deficiency and affected boys are only recognised in later infancy and childhood because of early signs of pseudoprecocious puberty. Prepubertal gynaecomastia is another feature peculiar to this enzyme defect. The clinical hallmark of 11β-hydroxylase deficiency is hypertension secondary to increased mineralocorticoid production. Hypertensive encephalopathy and cerebrovascular accidents are known complications but the severity of hypertension is unrelated to the degree of virilisation.[6] Hypertension is not a constant feature of 11β-hydroxylase deficiency, however, and is rarely present at birth.

Diagnosis

The newborn infant with ambiguous genitalia is a medical emergency and appropriate investigations must be started quickly. The problem is a distressing one for the parents and they must be given a careful explanation of what will be done to determine the sex of the infant and how long this will take. There must be no guessing at the sex. It is important to note that the commonest cause of ambiguous genitalia of the newborn is congenital adrenal hyperplasia and the commonest cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. To confirm this diagnosis two investigations are essential: measurement of plasma 17OH-progesterone concentration and determination of a peripheral karyotype A complete list of relevant investigations is shown in table 2.

The enzyme 21-hydroxylase is required for the conversion of 17OH-progesterone to 11-deoxycortisol in the pathway of cortisol biosynthesis. In its absence there is accumulation of 17OH-progesterone, which is readily measured in plasma. The test is rapid and reliable for the diagnosis of 21-hydroxylase deficiency.[7 8] The assay is available routinely through the supraregional steroid assay service and can be performed on filter paper blood spots as well as in plasma, saliva, and amniotic fluid. It is advisable to delay sample collection for 24 hours after birth to allow for the disappearance in 17OH-progesterone produced by the placenta. The steroid is a stress related hormone and concentrations can be very high in ill infants (particularly if preterm) without adrenal disease.[9] A repeat measurement of 17OH-progesterone when the infant is better or an assessment of the 17OH-progesterone response to adrenocorticotrophic hormone stimulation may be necessary to resolve the question of possible 21-hydroxylase deficiency in a male preterm infant with low plasma sodium concentrations.

The peripheral karyotype must always be determined in an infant with ambiguous genitalia or in a 'male' with bilateral cryptorchidism and hypospadias. A provisional result can be provided by most cytogenetic laboratories within 48 hours of lymphocyte culture. A definitive diagnosis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in a newborn infant with ambiguous genitalia can be made two to three days after birth based on a 46 XX karyotype and an increased plasma concentration of 17OH-progesterone (usually >200 nmol/l; normal <10 nmol/l in a full term infant). Other steroid concentrations known to be raised in 21-hydroxylase deficiency include 21-deoxycortisol, androstenedione, and testosterone. When the plasma 17OH-progesterone concentration is normal or only slightly increased, the concentration of plasma 11-deoxycortisol as an index of 11β-hydroxylase deficiency should be determined. Additional confirmatory evidence of this rarer enzyme defect can be obtained by measurement of specific steroid metabolites in urine using detailed gas chromatographic analysis.

Table 2 *Diagnostic tests for congenital adrenal hyperplasia*

Blood:	17OH-progesterone
	Testosterone
	Androstenedione
	Adrenocorticotrophic hormone
	Plasma renin
	11-Deoxycortisol (11β-hydroxylase defect)
	Karyotype
Urine:	17-Oxosteroids
	Pregnanetriol
	Gas chromatographic steroid profile
Radiology:	Pelvic ultrasound examination
	Vaginography
	Intravenous urography

Plasma concentrations of adrenocorticotrophic hormone are raised with both enzyme defects but the assay is available only in a few specialised centres. Ambiguous genitalia in an infant with a 46 XY karyotype is a complex problem requiring investigation by a paediatric endocrinologist.

At least two thirds of patients with 21-hydroxylase deficiency are salt losers. Typically they develop hyponatraemia, hyperkalaemia, azotaemia, early metabolic acidosis, increased urinary sodium excretion, and occasionally hypoglycaemia. Plasma renin activity is a more sensitive index of mineralocorticoid insufficiency and is increased soon after birth.[10] However, the results are seldom available immediately.

Early management

MEDICAL

The salt losing crisis in an infant with congenital adrenal hyperplasia requires treatment with intravenous normal saline, the amount being calculated based on the sodium deficit and the degree of dehydration. Glucose should also be infused because of the risk of hypoglycaemia. Hyperkalaemia may rarely be severe enough to require more immediate treatment with insulin. Unless there is peripheral circulatory collapse, glucocorticoids should be withheld until blood samples for steroid analyses have been collected. Glucocorticoid treatment can be started using a replacement dose from the onset; this will adequately suppress raised 17OH-progesterone concentrations within weeks. The alternative regimen of using a high initial dose of glucocorticoid is unnecessary and almost certainly adversely affects the normal rapid growth rate characteristic of early infancy. I favour the use of hydrocortisone (cortisol) as the preferred choice of glucocorticoid. It is the physiological hormone active in man, the cortisol secretion rate is standardised for surface area (about 12 mg/m^2/day),[11] and there is 50% consistent absorption of an oral dose. A dose of 20 mg/m^2/day is about 5 mg per day for an infant; this can be divided into dosages of 2·5, 1·25, and 1·25 mg given at intervals of eight hours. The pharmacist will need to prepare hydrocortisone in solution to prescribe such small amounts. An oral preparation of cortisol (Corlan, Glaxo) in the form of 2·5 mg hydrocortisone pellets designed for treating mouth ulcers can be prescribed after the first year.

Salt replenishment during the early salt losing crisis is usually adequately provided by intravenous saline. It is seldom necessary to use a parenteral mineralocorticoid preparation. Oral 9α-fludrocortisone (Florinef) is a potent mineralocorticoid which can be started in a dose of 0·1–0·2 mg daily once the infant is rehydrated and taking oral feeds. Occasionally higher doses are required but the blood pressure must be monitored regularly. Supplementing the oral feeds with 2–3 g of salt daily in divided doses until semisolid feeding is established is occasionally required.

Deoxycortisone pivalate is a long acting mineralocorticoid which, in a dose of 12·5–25 mg monthly by intramuscular injection, is useful for the rare patient in whom there is a problem with treatment compliance.

SURGICAL

The variable degree of virilisation of the external genitalia in girls with congenital adrenal hyperplasia has already been emphasised. It is essential for the infant to be seen early by a surgeon experienced in the techniques required for reconstruction of the genitalia. There are basically two structural abnormalities which require surgical treatment: reduction in the size of the enlarged clitoris and division of the fused labial folds to exteriorise the vaginal opening. The various surgical techniques used to perform the clitoroplasty and vagnioplasty are beyond the scope of this review. Some or all of the radiological investigations listed in table 2 should be performed before surgery. Only clitoroplasty is normally performed in infancy; unless there is evidence that the labial fusion and urogenital sinus is contributing to infection, it is preferable to delay vaginoplasty until the time of puberty. The parents should understand that the female internal genitalia are normally developed. Pictures from a pelvic ultrasound examination or vaginography to show the uterus and ovaries can be most reassuring. The sex of rearing for a girl with congenital adrenal hyperplasia should always be female, whatever the degree of virilisation.

Later management

Treatment in congenital adrenal hyperplasia should aim to ensure normal growth in infancy and childhood, the development of puberty at the appropriate age and later, the acquisition of adult reproductive potential. This goal needs to be achieved using the minimum amount of glucocorticoid required to suppress excess androgen production. There is a delicate balance to strike between the prevention of androgen induced rapid growth with advanced skeletal maturation on the one hand and the inhibition of normal growth from excessive glucocorticoid replacement on the other.

Several glucocorticoid preparations have been tried as regular replacement treatment in congenital adrenal hyperplasia. Their relative potencies in

Table 3 *Potency of steroid preparations used in congenital adrenal hyperplasia*

Steroid	*Potency*
Cortisol	1·0
Cortisone	0·8
Prednisolone	5·0
Prednisone	4·0
Dexamethasone	80·0
9α-Fludrocortisone	10·0

Cortisol is arbitrarily assigned a value of 1 for glucocorticoid potency

relation to cortisol (hydrocortisone) are shown in table 3. I favour the continued use of hydrocortisone throughout childhood and puberty until statural growth is almost complete. A dose as low as 12–15 mg/m^2/day is often sufficient but the treatment for each individual needs to be tailored according to age appropriate growth rates and various steroid indices of control (see later). The daily amount of hydrocortisone needs to be given in two or three divided dosages; it is customary to administer 50% of the daily dose at bedtime but there is no evidence that this achieves any better control. Cortisone acetate is usually equally effective but hepatic conversion to active cortisol may be unpredictable in some patients. Prednisolone is used by some to attenuate the pronounced rise in precursor steroid concentrations which occur during the night time hours.

When statural growth is complete, dexamethasone is an effective form of treatment to use in the long term. The longer biological half life (about three and a half hours) allows medication to be administered only once,[12] or at the most, twice daily Single daily medication should probably be given in the morning in a maximum dosage of 0·01 mg/kg/day or about 0·25–0·5 mg/day. The individual dosage requirement to achieve adequate control in congenital adrenal hyperplasia can be quite variable. Certainly the potency of dexamethasone relative to cortisol is about 80:1 rather than the figure of 30:1 quoted in standard texts. Treatment with dexamethasone is particularly effective in regulating menses and ensuring ovulation in postmenarchal women with congenital adrenal hyperplasia.[13] Other less conventional forms of medical treatment for congenital adrenal hyperplasia include the use of cyproterone acetate to block the tissue action of androgens and long acting analogues of luteinising hormone releasing hormone to slow down puberty in patients who have an advanced bone age.[14]

Most patients with 21-hydroxylase deficiency are probably salt losers if a sensitive index such as plasma renin activity is used to assess mineralocorticoid secretion.[15] A previous annotation in this journal recommended that mineralocorticoid replacement could be discontinued for salt losing infants in later childhood.[16] The practice is potentially dangerous as any reduction in an acquired high salt intake can precipitate an adrenal crisis. Mineralocorticoid replacement should continue as 9α-fludrocortisone in a daily dosage of 0·1–0·15 mg. When adequate mineralocorticoid treatment is given, improved linear growth often occurs.[17] The principles of glucocorticoid replacement in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency are the same. Suppression of the increased concentration of deoxycorticosterone, a potent mineralocorticoid, sometimes precipitates a salt losing crisis.

How should control be monitored?

Clinical parameters of control in congenital adrenal hyperplasia include measurement of growth velocity and skeletal maturation (bone age), signs of hypercortisolism (striae, weight gain, hypertension), and noting the pattern of menses in postpubertal women. These are essential to monitor regularly but the parameters are insensitive indicators of control in the short term and are of necessity, retrospective. Assessment of skeletal maturity is unreliable during infancy at a time when satisfactory control is essential if normal growth is to be sustained throughout childhood and adolescence. The outcome for adult height in the first generation of patients treated regularly with glucocorticoid replacement has generally been unsatisfactory.[18 19] Irregular menses and infertility in both sexes have been additional problems.

Several steroid parameters have been used to monitor adequacy of treatment in congenital adrenal hyperplasia. Urinary 17-oxosteroid and pregnanetriol excretion is an insensitive index of control and is seldom used now. Single random determinations of plasma 17OH-progesterone concentrations are difficult to interprete because of the combined influences of stress, an intrinsic circadian rhythm, and the timing of previous glucocorticoid medication on adrenal steroid hormone concentrations. A very high early morning concentration of 17OH-progesterone can fall to normal values by late afternoon even in a poorly controlled patient. The interpretation of a single estimation of 17OH-progesterone would clearly be quite different for samples collected in morning and afternoon clinics. The problem can be circumvented by the use of daily profiles of 17OH-progesterone. The availability to measure this steroid in filter paper blood spots and saliva makes it possible for frequent, serial samples to be collected at home by patients with congenital adrenal hyperplasia of all ages.

Pictorial nomograms of 170H-progesterone rhythms have recently been constructed to interpret the daily profiles of blood spot and saliva 170H-progesterone measurements in individual patients with congenital adrenal hyperplasia.[20] The magnitude of the circadian rhythm is an important index of control. The disappearance of the rhythm is an early sign of overtreatment. Table 4 contains examples of profiles typical of various categories of control in congenital adrenal hyperplasia. Plasma testosterone measurement is also a useful marker of control and can be used singly as the concentrations do not fluctuate as widely as 170H-progesterone. If daily 170H-progesterone profiles are not used, then a single plasma measurement of this steroid and testosterone at 0800 hours is often informative. Adequate control is indicated by 170H-progesterone concentration in the range of 30–70 nmol/l in blood, 260–1000 pmol/l in saliva, and plasma testosterone concentrations <0·5 nmol/l (prepubertal children) and between 1·0–2·5 nmol/l (pubertal females). Measurement of plasma testosterone is of no value in the pubertal male due to the increasing contribution of testosterone from the testis which occurs at this age. Androstenedione is also an index of adrenal androgen secretion and is an alternative marker to monitor control in congenital adrenal hyperplasia.[21 22]

Table 4 *Typical daily profiles of 170H-progesterone in congenital adrenal hyperplasia related to degree of control*

Time (hours)	*Undertreated*		*Adequately treated*		*Overtreated*	
	Blood	*Saliva*	*Blood*	*Saliva*	*Blood*	*Saliva*
0800	70–240	6000	30–70	1000	<10	500
1200	15–140	4000	<15	500	<5	<150
1800	10–100	2500	<10	200	<5	<150
2200	10–20	2000	<10	150	<1	<150

The values given are only guidelines Concentrations of 170H-progesterone in blood are in nmol/l and in saliva in pmol/l, respectively

Measurement of plasma electrolytes is an insensitive index of mineralocorticoid replacement in congenital adrenal hyperplasia. Sufficient mineralocorticoid should be prescribed to maintain levels of plasma renin activity within a range appropriate for age. This applies particularly during infancy when concentrations up to 20 pmol/ml/hour are observed for normal infants. Measurement of plasma 11-deoxycortisol and testosterone are indices of control in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency.

Prenatal diagnosis and treatment

Considerable information has been gathered on the genetics of congenital adrenal hyperplasia in recent years and the interested reader is referred to two excellent reviews of the subject.[23 24] Measurement of the concentration of 170H-progesterone in amniotic fluid collected during the second trimester of pregnancy is a reliable test for the prenatal diagnosis of 21-hydroxylase deficiency.[25] However, this is too late to prevent virilisation of an affected female by giving oral dexamethasone to the mother. HLA typing of amniotic cells can also be used for prenatal diagnosis but the method is technically more complex and the result may be misleading. Analysis of a chorionic villus biopsy using DNA restriction fragment length polymorphisms would allow earlier prenatal diagnosis. The current cDNA probes for the 21-hydroxylase gene, however, show homozygous deletions in only a minority of patients with congenital adrenal hyperplasia. The analysis does allow for earlier fetal karyotype determination which will affect the need for prenatal treatment. One option in the 'at risk' pregnancy is to start maternal dexamethasone treatment (0·5–1·0 mg daily) empirically as early as 5 weeks' gestation and discontinue treatment for 10 days before an amniocentesis is performed at 16 weeks for steroid estimation. Treatment can be restarted if the concentration of 170H-progesterone is raised and the fetus is female. There are only isolated reports of the success of this treatment. Generally, there is a reduction, but not a complete absence, in virilisation of the female external genitalia.

Newborn screening

The incidence of congenital adrenal hyperplasia based on several pilot newborn screening programmes is about 1 in 10 000 white births, but as high as 1 in 230 among the Yupik Eskimos. Measurement of 170H-progesterone in a filter paper blood spot sample is simple to perform. However, false positive results are sometimes observed in sick preterm infants. Table 5 lists the problems which are

Table 5 *Problems potentially avoidable with newborn screening for congenital adrenal hyperplasia*

Salt wasting crisis
Inappropriate diagnosis and treatment of 'pyloric stenosis'
Inappropriate gender assignment
Precocious puberty
Stunted growth
Sudden death

potentially avoidable if screening for congenital adrenal hyperplasia was practised routinely. Even so, the incidence of cases that would not be detected clinically must be very low. A retrospective survey of a large number of patients with congenital adrenal hyperplasia in Birmingham showed an improvement in early diagnosis in children born after 1970.[26] The authors concluded that in countries like the United Kingdom, where a rapid 17OH-progesterone measurement is readily available, neonatal screening for congenital adrenal hyperplasia was not necessary.

Conclusion

Congenital adrenal hyperplasia is an uncommon chronic disorder which will present in the newborn nursery only about once every two years even in the busiest maternity unit. A high clinical index of suspicion should be maintained for all infants with abnormal genitalia and boys who fail to thrive. The diagnostic tests are readily available and reliable. Treated patients should expect a normal life span and reproductive potential. This can be achieved by careful attention to regular measurements of clinical parameters of control and supplemented with the use of more modern and sensitive biochemical indices of control.

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Archives of Disease in Childhood, 1988, **63,** 1405–1407

Current topic

Controversies about intensive training in young athletes

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In the past few years increasing concern has been expressed about the possible harmful effects of intensive training in young athletes. In gymnastics, swimming, and tennis children in their early teens have already been undergoing intensive training and high level competition for some four or five years. Due to the increasing emphasis on competitive success it is widely believed that, in order to achieve a world class standard at senior level, it is necessary to commence intensive training well before puberty. This emphasis on early specialisation in a single sport with its accompanying intensive training and high level competition begs the following questions: have young children the physical, physiological, and psychological capabilities for intensive training and high level competition? Is there an increased risk of bony and soft tissues injuries in the developing musculoskeletal system?

Physical and physiological effects

The effects of training are difficult to separate from those of normal puberty.[1] Results are conflicting: some studies have described growth retardation,[2] and others no detectable effects.[3–6] Most studies conclude that a certain amount of physical activity is required for normal growth, but fail to identify what the minimum is and what, if any, are the disadvantages of intensive training.[1–6]

A topic of great interest is the age of achieving menarche and the incidence and duration of menstrual disturbances in young athletes engaged in intensive training. Malina concluded that, with few exceptions, menarche is delayed in athletes,[4] and Bonen and Keizer have identified an increased frequency of menstrual irregularities in female athletes.[5] The data dealing with this issue are limited, however, and not well controlled as they have not taken into account other factors that could influence the time of menarche, such as genetic influences or nutritional state.

Kotulan *et al* followed the skeletal maturation of young male athletes engaged in cycling, rowing, and ice hockey from 12 to 15 years and concluded that regular physical activity had no effects on their growth.

The training response of a given athlete is associated with an inherited genotype. It has been shown that about 30% of the final maximal oxygen uptake (VO_2 max) and maximal force and power of top class competitors can be accounted for by training.[7]

Ekblom found that young athletes undergoing vigorous training were taller, had less body fat, and higher VO_2 max than controls.[8] More recently Sundberg and Elovainio compared 34 boys aged 12–16 engaged in competitive middle and long distance running with 56 controls not undergoing intensive training.[9] The runners had been training for two to five years and tended to have less body fat and lower resting heart rate, but the difference only achieved significance at 16 years. At this age runners also had larger heart volumes, as assessed using a roentgengraphic method, and a higher VO_2 max relative to body weight and respiratory capacity.

Fournier *et al* studied the effects of sprint and endurance training on the vastus lateralis muscles of boys of 16 and 17 years.[10] They showed that endurance training resulted in an appreciable increase of type I and IIA fibre areas, together with increased activity of some of the enzymes of the Kreb's cycle Sprint training resulted in an appreciable increase in the activity of glycolytic enzymes only.

There have been a number of reports of a fatigue syndrome in top class athletes No controlled studies have been performed, however, and most are anecdotal in type. Possible mechanisms include an increased predisposition to viral infections, fatigue due to overtraining, or a combination of physical and psychological fatigue analogous to the 'burn out syndrome' reported in other contexts.[11–13]

Injuries

Because of the presence of growth cartilage, and the process of growth itself, the bones and joints of a young athlete are more prone to specific types of injuries.[4] In children ligamentous structures are two to five times stronger than the cartilage and the bone of the epiphysial plate to which they are attached[15 16] resulting in a greater likelihood of fracture of the epiphysial-metaphysial junction rather than the ligamentous tear more commonly seen in adults.

Overuse injuries are a condition characterised by chronic inflammation due to repeated microtrauma. Young athletes undergoing prolonged repetitive activity may develop osteochondrosis,[17] a group of diseases involving degeneration of the centre of ossification where a major tendon attaches to the apophysis of a bone. Common sites are the lower pole of the patella (Sinding-Larson-Johansson syndrome), the tibial tubercle (Osgood-Schlatter disease), the posterior aspect of the calcaneus (Sever's disease); the small carpal and tarsal bones may also be affected. Some studies have shown that young athletes are at greater risk of developing stress fractures, and, in childhood, compression stress fractures occur rather than the oblique type commonly seen in adults.[18 19]

After a careful analysis of training regimens it has been estimated that at least 60% of all injuries sustained were in direct relation to training and could be avoided by appropriate changes in training programmes.[14]

A central issue is whether an alteration of training regimen after an injury can maintain fitness and ensure rapid healing. Very little research has been performed in this area, although Moroz and Houston have recently shown that the replacement of endurance running with endurance cycling for four weeks can maintain maximal aerobic power and submaximal running performance for moderately trained women runners[20]

Psychological effects

The most serious concerns have been the increased stress and anxiety due to competition,[21] the influence of parents on performance,[22] and the incidence of aggression in young athletes.[23] These concerns have even led to a call for a complete ban on high level competitive sport in preadolescence because of the possible long term deleterious effects,[24] and have also resulted in a change in emphasis from competitive to participatory sports in some education authorities. Detailed reviews of the psychological effects of intensive training on young athletes have recently been published.[25 26]

Conclusions

Definitive statements about the effects of intensive training on young athletes cannot yet be made. Cardiovascular and muscular responses to training in children appear to be similar to those found in adults and, in the short term at least, would appear to be beneficial. Concerns about physical and psychological injury remain, however, and it is likely that the age of the child and the particular sport should influence the type and intensity of training.

Young athletes are not just smaller athletes, and they should not become sacrificial lambs to a coach's or parent's ego. Paediatricians and others dealing with young athletes should be aware of these concerns, and, until more definitive studies are performed, the 'not too much and not too soon' rule should apply, although it must be admitted that it remains unclear as to how much is 'too much' and how soon is 'too soon'.

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Archives of Disease in Childhood, 1988, **63,** 1408–1412

Regular review

Perthes' disease: growth and aetiology

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During the last decade it has become evident that Perthes' disease can no longer be considered as a local ischaemic disorder in an otherwise normal child.[1–3] The affected child's growth and development are unusual in several respects, namely (figure):

- Bone age[3–5]
- Stature[6–8] and growth velocity[9]
- Disproportionate skeletal growth[6 7]
- Hormones[10–12]
- Congenital anomalies and defects[13 14]
- The unaffected hip[3 13 15 16]

Considering the new evidence, Harrison and Burwell concluded that Perthes' disease is a force orientated hip lesion based upon a constitutional defect that affects growing bones.[3] Local and general disorders acting together result in a hip joint that is structurally inadequate for the loads that have to be borne, leading to a stress fracture.

The purpose of this review is firstly, to summarise what is known about the underlying growth pattern; and secondly, to present a synthesis of knowledge as a theory of aetiology.

General growth pattern

BONE AGING AT THE HAND AND WRIST

Skeletal immaturity at the hand and wrist of children with Perthes' disease is now accepted as part of the clinical picture. Most workers have performed cross sectional studies comparing their data with the Greulich and Pyle standards.[illegible] Recently, the application of the Tanner-Whitehouse (TW2) system has shown not only bone age delay but also dysharmony with the carpal, more retarded than the radius, ulna, and short bone age.[4]

In a longitudinal study, Harrison reported a 'standstill phenomenon' in some young affected children in which no new carpal bones are ossified,[3] although existing carpal bones grow in size.[4] This aspect is more extensively studied in boys and girls by Kristmundsdottir *et al*,[5] who confirmed a relationship between bilateral disease and severe bone age delay.

Some data are available for bone age at the knee (ME Blakemore, personal communication), but not at the foot or pelvis. What evidence there is suggests that the impaired skeletal maturation is unevenly distributed in growing bones and is most evident in distal limb segments. Brothers, but not sisters, of affected children also show bone age retardation at the wrist,[3] but it is unclear whether this is familial or community linked.

STATURE AND GROWTH VELOCITY

When the stature of children with Perthes' disease is plotted against bone age, most lie above the 90th centile. When stature is plotted against chronological age many workers find affected children have low-normal centiles, with only a small proportion lying below the 3rd centile.[6 8]

A longitudinal study of 12 affected boys shows retarded growth velocity soon after diagnosis, followed by a phase of catch up.[9] More work on growth velocity is in progress (DJ Hall, personal communication).[17] The onset of puberty is usually normal (DJ Hall, personal communication). By the age of 12–15 years, stature is normal[8] as also is bone age (DJ Hall, personal communication).

The parents and siblings of children with Perthes' disease are of normal height[7 8]; this suggests that any short stature is associated with the disease and is not of familial origin.

DISPROPORTIONATE SKELETAL GROWTH

A three centre study in the United Kingdom of children with Perthes' disease involving measurements of the head, trunk, and limbs shows a subtle dysmorphic pattern termed 'rostral sparing' (figure).[6]

The growth pattern includes a normal head circumference, no disproportion between sitting height and subischial height, a foot which is short relative to the tibia, and a forearm and hand short relative to the upper arm. Such limb patterns are

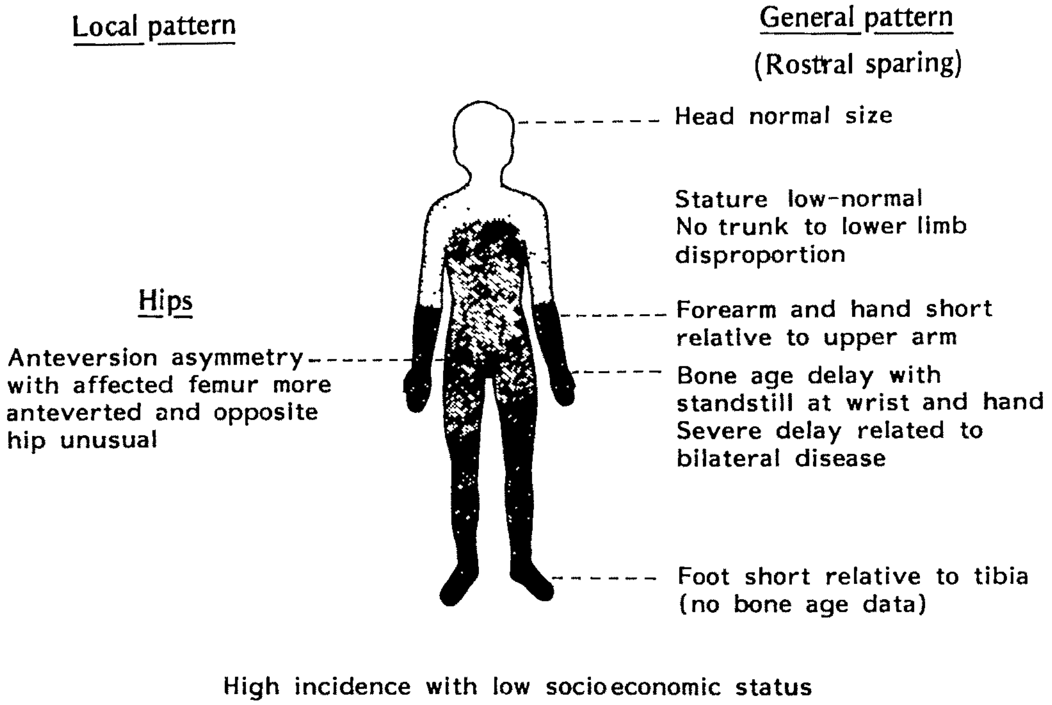
Local pattern
General pattern
(Rostral sparing)
Head normal size
Stature low-normal
No trunk to lower limb disproportion
Hips
Anteversion asymmetry with affected femur more anteverted and opposite hip unusual
Forearm and hand short relative to upper arm
Bone age delay with standstill at wrist and hand
Severe delay related to bilateral disease
Foot short relative to tibia (no bone age data)
High incidence with low socioeconomic status

Figure *Diagram to show the underlying general growth pattern in children with Perthes' disease.*[6] *The general growth pattern may be due to manganese deficiency in deprived groups of the population.*[28] *The local growth pattern at the hips involves femoral anteversion asymmetry with the more anteverted femur being affected by the disease.*[16]

found in the unaffected as well as the affected leg in children within two months of diagnosis and in girls as well as boys.

Recent work in Liverpool finds that children in families where Perthes' disease occurs have retarded growth of the trunk, with reduced sitting height and biacromial diameter. Among those who develop the disease there is also retarded limb growth, most evident as unusually small feet.[7]

The association of this limb growth pattern with Perthes' disease begs the question of whether it occurs in genetically predisposed individuals or indicates mechanisms involved in disease development.

HORMONES

The peak incidence of Perthes' disease at 4–5 years of age[13] occurs during the quiescent hormonal period.[10]

The bone age retardation in Perthes' disease is similar to that found in hypothyroidism, but in Perthes' disease there is no evidence of thyroid dysfunction.[11] The serum growth hormone response to insulin induced hypoglycaemia is significantly reduced in affected prepubertal boys compared with a control group of short boys.[11] Serum somatomedin measured by bioassays is raised.[10 11] In Japan, serum somatomedin A measured by a radioreceptor assay is reduced compared with a control group of normal children.[12] More work is needed, although any hormonal involvement is likely to occur at the tissue level[5] and may not be amenable to conventional endocrine investigation.

Local growth pattern

Is there any evidence of an underlying growth abnormality at the upper end of the femur which could make a child susceptible to the onset of Perthes' disease? Early work based on radiography showed increased anteversion in some children but not in others.[18] More recently, a new ultrasound method shows a subtle pattern of femoral anteversion asymmetry in most children with unilateral Perthes' disease; the affected hip is almost always the more anteverted; and the opposite femur has an anteversion pattern different from normal, possibly developmental (figure).[16]

Are these anteversion findings in children with Perthes' disease 'primary' or merely 'secondary' to the disease in the femoral head? Two findings suggest that the anteversion in the affected hip precedes the disease: namely, its presence at diagnosis and the changes in the opposite hip. More work, especially longitudinal, is needed to establish the point.

In healthy white children, anteversion asymmetry of 10 degrees or more is found in 10% of the normal population and there is no relation to social class.[19] In healthy *siblings* of affected children the mean femoral anteversion is normal; but below the age of 7 years there is an excess of siblings with anteversion asymmetry (SS Upadhyay, RG Burwell, PP Belliappa, MRK Karpinski, A Moulton, WA Wallace, unpublished observations).

Views on the general growth pattern

It is tempting to link the general growth pattern with the cause of the disease, but so far a theory of aetiology has proved elusive.[1-3] Several aspects need consideration.

(1) GENETIC PREDISPOSITION?

Genetic studies[8 20 21] and work on HLA antigens[20 22] produce conflicting findings. Hall's comprehensive review concludes that Perthes' disease involves multifactorial inheritance,[21] although a few families show evidence of autosomal dominance.

(2) SKELETAL DYSPLASIA?

Perthes' like changes in the hips are associated with certain congenital malformation syndromes,[14 23] the closest to Perthes' disease being acromesomelic dwarfism.[24]

The general growth pattern of Perthes' disease was at first considered to result from an abnormality of the mechanisms that control differential growth rates in the various regions of the body—determined by environmental factors with or without additional genetic factors acting during embryonic life.[6]

In the growth plate of each normal bone there may be a time tally that controls body proportions with age.[11] Abnormalities of this time tally system in children with Perthes' disease could account for their pattern of skeletal shape distortion. The hypothesis of a time tally in growing bones needs experimental evaluation in animals using recombinant grafts. The problem is part of the wider concept of homeotic genes, which control regional development in the body now being studied experimentally in insects.

(3) MALNUTRITION?

In infant monkeys malnutrition leads to impairment of head growth and of distal limb growth.[25] The latter finding for the limbs is remarkably similar to that seen in Perthes' disease[3]—the diagnosis of which is made after the child's head has grown rapidly in the first two years of postnatal life. In the case of the monkeys, Fleagle *et al* suggest the hypothesis that the more advanced skeletal region is always the one in which growth is most affected by malnutrition.[25] Hence, blood borne factors altered by nutrition could determine the general growth pattern seen in children with Perthes' disease.[3]

Undernutrition may have relevance to the geographical variation of Perthes' disease in the United Kingdom, with a high incidence in children from families of low socioeconomic status.[26] The highest annual incidence recorded to date is 21·1/100 000 children younger than 15 years of age in the inner city of Liverpool, England; the disease is uncommon in the rural areas of Lincolnshire and East Yorkshire.[27 28] Barker and Hall conclude that Perthes' disease may have major determinants acting at a critical stage of early life before the age of 2 years[26]—but this timing would not explain the normal head size.[6]

What these determinants may be is unknown, but microdeficiences may be at work,[5] and particularly manganese deficiency [28]

(4) MANGANESE DEFICIENCY?

Manganese deficiency results in skeletal and postural defects in many species of animals. Shortening of limb bones relative to the trunk occurs in manganese deficient rats; this has been attributed to abnormal cartilage and bone matrix formation particularly of chondroitin sulphate.[29 30]

The importance of such experimental findings for normal human development is unknown. Preliminary research, however, predicated on the underlying growth pattern,[6] indicates that children with Perthes' disease may be manganese deficient.[28]

Unifying theory of aetiology

LOCAL DYSHARMONY BETWEEN CARTILAGE AND BONE

Current evidence is consistent with the view that at the time of diagnosis of Perthes' disease there is dysharmony between cartilage and bone in at least two regions of the skeleton: (a) at the *wrist,* in which existing bones grow slowly and some cartilage models have delayed onset of ossification; and (b) at the *hip*, where thickened epiphyseal cartilage[31] may precede necrosis of the ossific nucleus.[32] The thickened cartilage and enlargement of the femoral head in Perthes' disease is generally attributed to epiphyseal growth being sustained by synovial fluid in the presence of an ischaemic ossific nucleus.[13 33]

In this connection, transient synovitis of the hip does not seem to be linked causally to Perthes' disease.[16 33 34]

The finding of skeletal dysharmony, particularly in the carpus at the time of diagnosis, implies the presence of a latent (incubation) period before the disease is expressed clinically.[2 5 20] The fact that Perthes' disease almost never recurs shows that the conditions that cause the disease are present at only one phase in the child's development.[35]

The earlier development of bilateral disease and its association with severe carpal delay suggests that a systemic blood borne factor contributes to the changes in both the hips and the wrist.[5]

What such a systemic factor(s) might be is unknown. It could be an essential substance in limited supply (hormone, nutrient, metabolite) or a deleterious agent.[20 28] The evidence suggests the hypothesis that during the quiescent hormonal period[10] a blood borne factor (possibly involving manganese[28] is essential for the production of a cartilage that will ossify.

SELECTION TO MORBIDITY

The simplest explanation (Occam's razor) for the underlying growth pattern is that normal young children with anomalous extremes of femoral anteversion asymmetry from all social classes are at risk of developing Perthes' disease: but only those with a disturbance in a systemic, blood borne factor develop the disease.

BLOOD BORNE FACTOR

According to this view of aetiology, a blood borne factor is responsible for the *bone age delay at the wrist* and the *short foot*—both of which are affected because of their acromelic development status.[5 25]

To account for *disease at the hip,* a sequence of mechanical and blood borne factors acting during the latent period is needed, such as:

(1) Increased dynamic mechanical stress in the more anteverted femoral head during gait and physical activity.[36 37]
(2) Increased epiphyseal cartilage turnover in the femoral head[38]—like the effect of intermittent physiological pressure on bone, growth plates, and healing articular cartilage.[39 40]
(3) Replacement of normal epiphyseal cartilage during the latent period by a less ossifiable cartilage—that also occurs at the carpus[18 41 42]—and both involving local tissue regulatory factors.
(4) Dysharmony between cartilage and bone growth results in more cartilage,[31] less bone, and a larger femoral head[13] with altered mechanical properties.
(5) Reduced mechanical strength of the femoral head[43] relative to the weight and physical activity of the child leads to stresses within the ossific nucleus[32] and a stress fracture with secondary vascular compromise.[3]
(6) Natural history is determined by the balance between: (a) loading at the hip and repeated stress fractures with vascular occlusions[44]; and (b) replacement of the epiphysis ultimately by normally ossifying cartilage.

Perspective

Although far from complete the morphological, auxological, epidemiological, and essential trace element studies have brought Perthes' disease to the stage at which some insight into aetiology is now possible.

Research is needed in four directions: on populations at risk; on patients and their families; clinical and laboratory studies on the biomechanics of hips with femoral anteversion asymmetry; and experimental models in animals.

The ultimate aim is prevention. As a bonus, aetiological mechanisms unveiled for Perthes' disease may provide a paradigm for some of the other osteochondroses of youth.

The writer thanks the National Fund for Research into Crippling Diseases (ACTION) for financial support, Professor RE Coupland for some facilities and Dr DJ Hall, Mr MHM Harrison, FRCS, Dr DI Johnston and Mr A Moulton, FRCS for helpful discussions

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Neonatology—then and now

The Editors have asked Dr Colin HM Walker to write the next series of short historical articles for the Journal Dr Walker has recently retired from his post as consultant paediatrician with a special interest in neonatology at Ninewells Hospital and Medical School, Dundee. His extensive contribution to the clinical care and research of the newborn will provide the perspective we seek. He has chosen subjects of current interest and looked back for articles on similar or related topics published in the Archives 20–30 years ago.

Bone injury—accidental or otherwise? (1958)

Traumatic subperiosteal haematoma of the femur in the newborn

ROSS G MITCHELL AND K RHANEY

University of St Andrews, Dundee (*Arch Dis Child* 1958;**33**:205–9)

Not many cases of this condition had thus far been reported and the authors present two, one of which provided the first necropsy description of this lesion. The paper starts:

> 'The occurrence at birth of a subperiosteal haematoma without fracture was not widely recognized until attention was drawn to the condition by Snedecor, Knapp and Wilson (1935), who called it 'traumatic ossifying periostitis'. A few other reports of this type of birth injury were subsequently published under such titles as periosteal stripping (Burman and Langsam, 1939), neonatal contusion (Caffey, 1945) and ossifying haematoma (Brailsford, 1948) ...'

The history of traumatic (usually breech) delivery leads one to suspect this diagnosis though, as this paper indicates, there is an important and considerable differential diagnosis when the lesion is detected in the immediately postneonatal period. This includes the normal double contour of the long bones (most frequently seen in preterm infants), infantile cortical hyperostosis, osteomyelitis, and congenital syphilis, and if discovered somewhat later—sarcoma, scurvy, and hypervitaminosis A. Most of these are relatively easy to distinguish from neonatal subperiosteal haematoma by the age of onset and other clinical findings.

Today. The present day interest in this entity is, however, found at the end of the section on differential diagnosis where it states:

> '...subperiosteal haematoma may follow comparatively minor trauma in postnatal life. ...''

It is not surprising that possible child abuse does not appear as a differential diagnosis as these two cases were diagnosed very early and at the time this paper was published little had been written on this subject. Today, however, trauma, accidental or otherwise, would come readily to mind on the finding in early infancy of radiological evidence, new or old, of subperiosteal haemorrhage. As a manifestation of birth trauma this lesion, like so many other forms of birth injury, has virtually disappeared, especially where breech extraction is avoided by the ready recourse to caesarean section. Where such obstetric care is not readily available, however, the possibility of periosteal lesions resulting from birth trauma and being first detected in early infancy must remain in mind.

The diagnostic differentiation of trauma from osteogenesis imperfecta in one of its less dramatic forms is difficult and the several varieties of the latter were also not recognised in the 1950s. Old traumatic lesions cause diagnostic problems and it has been recorded that 12% of parents on a United Kingdom register of 773 children with osteogenesis imperfecta were accused of non-accidental injury.[1] The exact age of old lesions is not easy to determine—yet another reason for caution in assuming these constitute evidence of child abuse in early infancy.

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Ross G Mitchell, an Edinburgh graduate, assumed the Chair of Child Health in Aberdeen after a consultant appointment in Dundee. He returned to the James Mackenzie Chair in Dundee in 1973 from which he retired in 1985. His abundant contributions to paediatric literature include reports on his earlier laboratory research, clinical practice, and author/editorships, notably the later additions of Ellis's *Disease in Infancy and Childhood* and his own *Child Health in the Community*. He still holds the position of chairman of the Mac Keith Press. His travels as consultant and speaker have taken him to all corners of the globe including Russia and Third World countries. He has served on numerous local and national medical committees, notably as Dean of the Faculty (Dundee), chairman of the Paediatric Advisory Committee, Scottish Home and Health Department, and member of the General Medical Council.

Dr Ken Rhaney, a paediatric pathologist, pioneered much in the field of neonatal morbid anatomy and histology.

Technical editor's note

From January 1989 results and measurements in the *Archives of Disease in Childhood* will be given in SI units only. Would contributors please ensure that all results in manuscripts, tables, and figures submitted from now on are in SI units otherwise publication may be delayed Exceptions to this are:

(a) Blood pressure in mm Hg;
(b) Ventilation pressure in cm H_2O;
(c) Concentration of drugs;
(d) Concentration of any substance where the molecular weight is not known accurately.

No old units or conversion factors should be submitted in manuscripts: conversion is the responsibility solely of the author

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British Paediatric Association

Annual meetings

At York University
1989 April 11–14

At University of Warwick:
1990 April 3–6
1991 April 16–19
1992 April 7–10
1993 April 20–23 (provisional)
1994 April 12–15 (provisional)

Archives of Disease in Childhood, 1988, **63,** 1415–1418

Correspondence

Monitoring for central apnoea in infancy—limitations of single channel recordings

Sir,

We were interested to read the article by MacFadyen *et al* on how the detection of 'central' apnoea (pauses in breathing movements) can be improved by using two respiratory channels.[1] The statement that 'breathing movements with amplitudes less than 25% of those at rest were considered not to be associated with appreciable ventilation' is not substantiated. To have done so would require concurrent measurement of one or more of the following: airflow into and out of the lungs, oxygenation, and carbon dioxide concentrations In our opinion, non-invasive monitoring of the arterial oxygen saturation (SaO_2) with pulse oximetry[2] provides more relevant data than a second channel of respiratory movements Experience with long term recordings of SaO_2, breathing movements, electrocardiography, and respiratory airflow indicates that 'central apnoea' may be less important than falls in oxygen saturation which occur with continued breathing movements (see figure)[3] Moreover, a recent evaluation of the volume expansion capsule transducer applied to the abdomen has found it to be an excellent indicator of breathing movements in infants under 6 months of age[4]

Many readers may misinterpret the fact that in fig 1–4 the graph papers upon which each signal is printed are malaligned We also have used their analysis system and therefore know that this may occur despite time synchrony of the signals We would, however, question the abdominal breathing movement signals in fig 4 before the purported episode of 'abdominal apnoea'. It is clearly asynchronous with both the electroencephalogram and thoracic impedance signals, therefore casting doubt upon the adequacy of attachment of the volume expansion

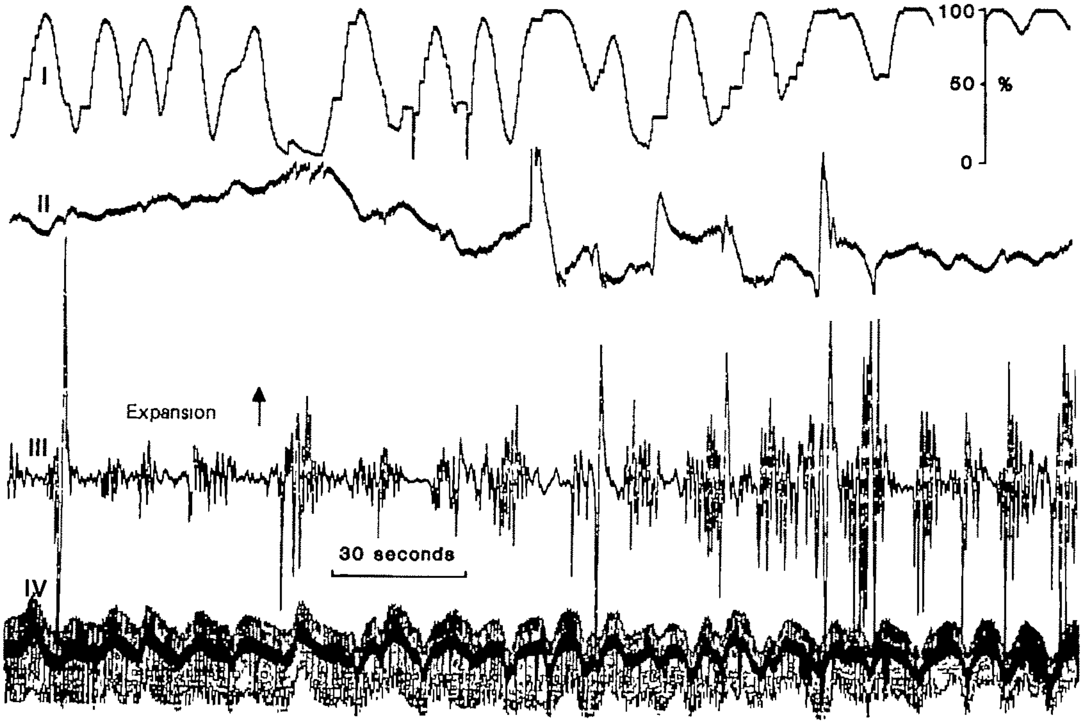

Figure *Cardiorespiratory monitoring of a 3 month old infant showing arterial oxygen saturation in beat-to-beat mode (I), the arterial pulse waveform from which the oxygen signal is derived (II), the abdominal expansion capsule (III) and electrocardiography (IV). Recording breathing movements and electrocardiotherapy alone would fail to identify gross hypoxaemic episodes which were not evident clinically* capsule and its consequent detection of breathing movements

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Dr MacFadyen comments

Our paper was written to draw attention to the possible inaccuracy of conclusions drawn from data which rely on a single channel recording as an indicator of respiration. We suggest that use of two separate channels reduces false interpretation of occurrence or duration of periods of absent movement on only one of the channels. We state clearly that we do not attempt to extrapolate from our observations to the possible significance of such pauses and caution against conclusions drawn from such extrapolations by others.[1] The use of indicators of oxygenation is an entirely separate issue. We recognise the continuing advances in non-invasive monitoring but reiterate the need for critical interpretation of data from any type of recording

Malalignment of electrocardiographic graph paper on reproduction does not alter the finding that duration of apparent apnoea was misleading if based on the single abdominal channel. The pressure capsule was properly applied and yielding consistent signals during quiet breathing as described in the paper On critical review of literature on interpretation of respiratory movements in most cases, including Dr Southall's work, an arbitrary threshold for significant movement or absence of movement is applied. As we describe in the methods section, applying an arbitrary threshold to interpretation of our recordings yielded an even higher rate of false positives for apnoea. Our stated conclusion holds true—the use of two channels of respiratory movement is less prone to qualitative and quantitative error than one, not that we have found an ideal foolproof indicator of apnoea and its significance

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Mercury as a health hazard

Sir,

I was very interested to read the case report of Pink disease (acrodynia) in a boy aged 18 months,[1] and the subsequent letter by Nicoll[2] reminding us that mild cases of mercury poisoning may look remarkably similar clinically to 'deprivation hands and feet' in severely disadvantaged children [3] I was reminded of a case in which the source of the intoxication was topical 1% ammoniated mercury used by a dermatologist for the treatment of eczema.

Case report

A girl, born at term, weighed 2500 g. She was breast fed for six months and then weaned onto cows' milk; cereals were introduced at three months. Her development was normal She was first seen aged 5 months because of her abnormal skull shape and severe infantile eczema, which had been treated with fluocinolone acetonide 0·01% for three months. There was a strong paternal family history of infantile eczema.

On examination she was a well nourished baby, weighing 6240 g. In addition to her plagiocephaly she had active eczema of her face, behind the ears, in the antecubital and popliteal fossae, and over the lower legs and ankles with numerous crusts over her scalp

She was treated with topical oilatum emollient and Unguentum emulsificans, and oral chlorpheniramine and promethazine. Her skin and cradle cap cleared rapidly, although cotton gloves were essential to prevent excoriation. One week after her discharge home at the age of 6 months her eczema flared up, and she was referred to a dermatologist who prescribed Arachis oil and 1% ammoniated mercury applications to the face. in addition to fluocinolone acetonide 0·01%. At 7 months of age she weighed 6520 g and her cheeks were noticeably red and by 8 months she had lost weight (6450 g) She was readmitted to hospital at 9 months when her weight had fallen further to 5500 g She was an unhappy infant with a swollen red upper lip and intense redness and irritation of the skin with red swollen hands and feet which felt paradoxically cold and clammy. She was reluctant to feed, miserable, and very irritable with appreciable photophobia. Her throat was infected and both tympanic membranes were pink. She showed moderate hypotonia associated with diminished reflexes. She also developed watery diarrhoea and required tube feeding to maintain her nutrition

On investigation her haemoglobin was 120 g/l, total white cell count 14×10^9/l (neutrophils 43%, lymphocytes 35%, monocytes 5%, eosinophils 15%, and basophils 2%) and the blood film showed slight anisocytosis and microcytosis. Concentrations of serum electrolytes, including calcium and phosphate, and serum proteins were normal, as was a culture of nasal and throat swabs and mid stream urine. Stool culture grew no enteric pathogens.

Her symptoms and the fact that she was being treated with 1% ammoniated mercury suggested that this might be Pink disease and further applications were stopped immediately. At 10 months of age she weighed 5730 g and the mercury concentration in her urine was 798 nmol/l (normal range 0–75 nmol/l) She was treated with penicillamine 62·5 mg three times a day for 14 days; during this time her urine mercury concentrations fluctuated between 548 and 848 nmol/l. As expected this concentration fell very gradually and two months later (aged 1 year) it was 75 nmol/l. By this time her weight had increased to 6030 g. Her subsequent development was that of a normal happy girl who was difficult to feed initially.

In Martindale (1982) we are reminded that 'mercury or mercurial preparations should not be given to infants or applied to their skin as they may cause acrodynia'. *Meyler's Side Effects of Drugs* indicates that 'the use of mercury in dermatological therapy should be abandoned'.[4] Although no mercury preparations are listed in MIMS, I note that ammoniated mercury powder and mercuric chloride are listed in the *Drug Tariff* (1987) (DHSS), the *American Hospital Formulary Service Book* (1988), formulations are also found in the *Pharmaceutical Codex* (1977), which is still current.

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Protective effect of BCG vaccination in infant Asians

Sir,

I read the article by Packe and Innes with special interest because I have been involved in BCG vaccination of Asian children both in this country and in India.[1] I am really surprised with their findings that BCG has a significant protective effect on Asian children as my own experience has been very disappointing.

In Patna, India, I followed up 90 children of the age group 1–12 who were found to be negative on prevaccination tuberculin testing and who did not show an accelerated reaction to BCG in the first seven days (BCG negative). All children were vaccinated by intradermal injection of 0·1 ml of reconstituted BCG vaccine supplied by BCG Laboratory, Madras, India, which uses the Danish 1331 strain of BCG. On serial tuberculin testing with 1 tuberculin unit (purified protein derivative, RT23 with Tween 80) every six months, I found that postvaccination tuberculin sensitivity appreciably decreased over an 18 month period (table)

Out of these 90 children six had developed tuberculous disease by 18 months. The criteria for diagnosis of tuberculosis in BCG vaccinated children were: (1) conversion of tuberculin negative child to positive; (2) increasing graduation of tuberculin reaction to greater than 10 mm; and (3) enlarged parahilar lymph nodes with or without parenchymal lesion on a chest radiograph. These findings made me think that immunity conferred by BCG is transient and probably does not last more than 18 months. Two years later (1982) while vaccinating school children in Blackburn I was not surprised to see that many school age Asian children had more than two BCG scars on their left deltoids and were still tine test negative. Other workers with BCG in developing countries have also had similar experience. Murtagh in Papua New Guinea found that 73·7% of the bacteriologically and histologically proved cases had already had BCG—some of them more than once [2] The largest controlled field trial ever done on BCG in Southern India did not show any protective effect.[3]

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Drs Packe and Innes comment:

In his letter, Dr Singh raises a number of important issues regarding the efficacy of BCG vaccination It is noteworthy that the results of studies on BCG vaccination in the newborn and in infants are more encouraging and consistent than are the results of BCG studies in older children and young adults (of which the South India study was a prime example).[1] This view is reinforced by the results of several recent studies sponsored by the World Health Organisation and by the results of our own study on infant

Table *Decreasing number of tuberculin positive cases after BCG vaccination (n=90)*

Tuberculin reaction	*No (%) of cases after six months*	*No (%) of cases after 12 months*	*No (%) of cases after 15 months*
More than 10 mm (positive cases)	54 (60)	33 (37)	19 (21)
Less than 10 mm (negative cases)	36 (40)	57 (63)	71 (79)

Asians in Birmingham, which show that BCG vaccination confers useful protection against tuberculous disease.

A discussion about why BCG in the newborn should be more effective than vaccination in older children and adults is outside the scope of this letter. One possibility, however, is that children given BCG vaccination soon after birth or at birth are not exposed sufficiently long to environmental factors which might mitigate the effect of BCG vaccination. For example, in areas where infection with atypical mycobacteria is common, such an infection before vaccination might provide a level of immunity comparable with that provided by BCG. This naturally acquired immunity might nullify or even oppose the effect of BCG vaccination.[1]

Dr Singh's results are in accordance with previous studies showing that tuberculin skin sensitivity induced by BCG vaccination diminishes with time. However, his interpretation of the results may be at fault because he makes the commonly made but erroneous assumption that tuberculin sensitivity equates with immunity against tuberculous disease. Indeed, there is evidence suggesting the absence of an association between tuberculin sensitivity and immunity.[2] Although it is likely that the protection conferred by BCG wanes with time after vaccination, it does not necessarily diminish at the same rate as tuberculin sensitivity.

In his study, Dr Singh found that 6·7% (6/90) of his vaccinated subjects developed tuberculous disease by 18 months after vaccination. These results presented in isolation do not argue against the efficacy of BCG vaccination. If, for example, the incidence of tuberculosis in unvaccinated subjects in the same community over a comparable period was significantly higher than that in the vaccinated group it would strongly suggest that BCG was exerting a protective effect.

Similarly Dr Singh quotes a study in which 73·7% of proved cases of tuberculosis in a population had received BCG vaccination, and cites this as evidence against the efficacy of the vaccine. Again, this information alone is inadequate to reach any conclusion about the efficacy of BCG. In his quoted example, if 90% of the total population had been vaccinated, the estimated protective efficacy of the vaccine would still be 68·9%—a level sufficient to justify its continued use. This result is difficult to grasp intuitively but can be better understood by reference to the paper by Smith.[3]

We firmly believe that routine BCG vaccination of the newborn and infants is a valuable preventative measure in communities where there is a high incidence of tuberculous disease.

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Incidence of zinc and copper deficiency in Japan

Sir,

This correspondence is concerned with the report by Shaw,[1] in which copper concentrations of infant formulas were cited from data by Lonnerdal *et al* as being 60 μg/l in Japan and 120–680 μg/l in other countries.[2]

In 1983, we sent questionnaires to 662 hospitals concerning zinc and copper deficiency from 1978–83. Three hundred and thirty five (51%) replied, of which 86 had treated children with these deficiencies. Further detailed answers were obtained from 40 out of these 86 hospitals (47%); deficiency for zinc was recorded in 76 cases and for copper, 11 cases. For those with zinc deficiency, 43 were under 6 months of age and 14 were aged 6 months to 1 year. Thus most of the patients (57/76, 75%) were under 1 year of age. Of the 76 patients, 17 were premature infants, 33 had intractable diarrhoea, 12 were on parenteral nutrition, two had inherited acrodermatitis enteropatica, and 12 had other complaints. Only two premature infants and none with intractable diarrhoea were fed breast milk. Of those with copper deficiency, two were below 6 months of age and seven were aged 6 months to 1 year. Like the infants with zinc deficiency these infants were mostly (9/11, 82%) under 1 year of age. At the time of this survey, the contents of zinc and copper in commercial formulas were 0·81–1·82 mg/l and 30–80 μg/l, respectively, as reported by Lonnerdal *et al.*[2] Since 1984, when the Japanese government accepted the addition of zinc and copper to infant formulas up to the concentrations recommended by the Food and Agricultural Organisation/World Health Organisation (3·2 mg/l zinc, 300 μg/l copper), the number of cases of zinc and copper deficiency has been dramatically reduced. Only five cases of zinc deficiency and no cases of copper deficiency have been recorded in the last three years among the same 40 hospitals concerned with the first survey.

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Archives of Disease in Childhood, 1988, **63,** 1419–1420

Book reviews

Harries' Paediatric Gastroenterology. 2nd ed. Edited by P J Milla and D P R Muller Pp 601 £50 hardback. Churchill Livingstone, 1988 ISBN 0-443-03058-8.

John Harries is described by his colleagues, he editors of this second edition, as 'a remarkable man who showed us that clinical practice combined with laboratory esearch could be stimulating, rewarding and above all, fun' All of us who ever worked with him can only agree and this book echoes those qualities

It has been greatly expanded and now ncludes among its contributors several distinguished transatlantic gastroenterologists The first of its four sections deals with basic science and investigatory techniques; he second and third contain a series of ndividual contributions on particular clinical problems involving the alimentary tract and liver, the final part deals with oral and parenteral nutrition. The editors claim it is primarily written with general paediatricians n mind Their objective is fulfilled in so far as it provides comprehensive coverage and horough bibliographies of the subjects dealt with. Individual references are as ecent as 1987. Those of us who deal only occasionally with patients suffering from chronic inflammatory bowel disease or chronic liver disease, for example, can use his work to tap the brains respectively of Richard Grand and Ian Booth and of Alex Mowat.

Alan Lucas provides an excellent update on gut hormones and adaptation to extraterine nutrition Common conditions are not ignored with chapters on surgical emergencies, irritable bowel syndrome, and acute and protracted diarrhoea

If there is any caveat, it is that the rigid ature of any system specialty means that diseases which cross systems may be dealt with less thoroughly. Ill defined conditions, such as food intolerance, which have not et landed themselves squarely in any articular specialty, are dealt with rather nervously by a number of contributors It is kely still to be in fashion by the third dition so let's hope it merits its own hapter. As with all multiauthor works, some chapters are more analytic than others For example, the possible relationhip of anal fissure and child sex abuse is mentioned in a single sentence referring to Hobbs and Wynne's work but without any discussion

This is a first rate book It deserves a place in every paediatric ward library just as John Harries deserves a place in our hearts

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Paediatric Gastroenterology. 2nd ed Edited by C M Anderson, V Burke, and M Gracey Pp 917 £95 hardback Blackwell Scientific Publications, 1987 ISBN 0-867-93176.

This is the largest of three new editions of paediatric gastroenterology textbooks published in 1987. Like its first edition 13 years ago *Paediatric Gastroenterology* by Anderson, Burke, and Gracey, aims to be a comprehensive reference text dealing with normal and abnormal function of the child's gastrointestinal tract Its 18 contributors are senior figures in paediatric gastroenterology, able to give illuminating historical introductions to their sections and to write from large and long personal experience Carre's description of hiatus hernia, for example, includes a study of 710 children, 80 for more than 30 years

Chapters on the oropharynx, oesophagus, and stomach (Carre, Dodge) thoroughly review their physiology and disorders A valuable chapter on endoscopy will require an additional section on endoscopic retrograde cholangiopancreatography in future editions There is an excellent review of small bowel physiology, with leading authorities (Walker, Burke, Auricchio, Brueton, Gracey) discussing development, digestion, brush border enzymes, immunology, and microflora, respectively Infective diarrhoea and gut infection and parasitisation (Gracey, Burke, Grove, Keusch) are rightly given prominence Professor Anderson writes with authority upon the approach to the child with abnormal stools, and on coeliac disease, cystic fibrosis, and inflammatory bowel disease Chapters on the radiology of the gut (Astley, Gates) and on the pancreas (Hadorn, Munch) were particularly good.

Inevitably the critical reviewer can find some omissions, such as the role of pH studies and of cisapride in gastro-oesophageal reflux, and some topical areas which merit fuller discussion, such as the use of rice powder in rehydration solutions and of elemental diets in the treatment of Crohn's disease The description (and picture) of a baby chair for postural treatment of reflux rather than the prone position will irritate some oesophagologists Books on the gut traditionally include a section on the liver (although the converse is not true) so setting the contributor the impossible task of providing a comprehensive review of a major specialty in one chapter

Despite these quibbles, this is an invaluable reference book for the practising paediatrician faced with a gastroenterological problem, and its value is enhanced by its thorough and recent literature citations and by excellent illustrations It is undoubtedly an essential medical library purchase I hope the third edition will be less tardy

M S Tanner
SENIOR LECTURER IN CHILD HEALTH
University of Leicester

Child Sexual Abuse Within the Family: Assessment and Treatment. Edited by A Bentovim. Pp 319: £19·50 softback. Butterworth Scientific, 1988. ISBN 7236-0634-X

A timely book on an unspeakable and hidden problem, which helps to break the taboo that sex abuse must not be talked about There is an extremely good opening chapter on definitions and normal sexual behaviour both in children and adults. I found the chapter on family functioning complicated and also naive, with little recognition of the fact that perpetrators by and large suffer from a compulsive behaviour disorder; an addiction, and go on abusing until they cannot get away with it. Many really prefer sex with children.

The chapter on recognition and assessment was good apart from the medical section, which I thought rather overlooked the holistic assessment (emotional behaviour, developmental as well as the general and specific physical forensic examination); and concentrated rather more on the 'knicker up/down' approach. Certainly they did emphasise that buggery is much more common than previously suspected, as is sexual abuse of boys.

The chapters on helping young children describing their experiences and family assessments were good The chapter on the group therapeutic work is excellent, and with further experience in the field, may produce part of a therapeutic input that indeed may have great influence on family healing.

In summary, patchy, but quite excellent in part.

H Richardson
CONSULTANT PAEDIATRICIAN
Community Health and Mental Handicap Services, Canterbury

A Practical Approach to Pediatric Otolaryngology. By C M Myer III and R T Cotton. Pp 247. £23·50 paperback. Wolfe Medical, 1988. ISBN 0-8151-1865-1.

There are very few books available specifically on paediatric otolaryngology which is, perhaps, surprising in view of the number of children who present to general practitioners and paediatricians with disorders of the ear, nose, and throat. Myer and Cotton have produced a readable book which all doctors who look after children will find useful. They sensibly assume a low level of basic knowledge and the first chapter is devoted to the anatomy of the relevant structures and their examination After this is a brief chapter on audiological examination that summarises the methods available and emphasises their shortcomings, particularly in very young children. The remainder of the book deals with disorders of the ear, nose, and throat in a problem orientated way. As well as chapters on otitis media, nasal obstruction, dizziness, and other topics one would expect to find, the authors have extended their brief to include sections on language disorders, facial paralysis, and salivary gland disease. The result is a comprehensive, though not exhaustive, book that encourages a logical approach to the disorders encountered in everyday practice and perhaps most importantly, indicates when specialised help should be sought.

The book has few failings. All the illustrations are in monochrome and of generally good quality but photographs of the tympanic membrane and of the larynx would have been greatly enhanced by colour. There are several useful algorithms but it is difficult to follow some of these because of their small print size There is an otherwise useful chapter on facial trauma in which no mention is made of non-accidental injury and its characteristic physical signs Nevertheless, I would recommend this book to general practitioners and the libraries of paediatric and accident and emergency departments.

J R James
LECTURER IN PAEDIATRICS
Leeds General Infirmary, Leeds

Assuring Quality Out-Patient Care for Children. Guidelines and a Management System. By C D Cook and J Heidt. Pp 197· £27·50 hardback Oxford University Press, 1988.

Although readable and interesting, the title of this American book is misleading. It bears no relationship to my own hospital outpatient practice It is about a computerised management system that involves guidelines, decision trees, structured encounter forms, and parent education material—for acute conditions that are usually dealt with in this country at the primary care level or as a direct acute hospital admission. It costs $35 000 per hospital to implement and $7 85 per case!

The book is based on the authors experience of this system in a downstat New York paediatric ambulatory car service, which is dealing with 200–600 wal in patients daily. The patients often had t wait up to six hours to be seen by the nex available paediatrician of whom there ar over 100 working in a given month! Eight per cent of the patients present with eithe upper respiratory infections, pneumonia diarrhoea and vomiting, acute abdomina pain, urinary tract infections, wheezing, o seizures The whole book, therefore, i directed solely at these disorders.

Although an immense amount of wor has been achieved, the approach is typicall American—for example, the decision tree are branched with cut off values for age specific temperatures, and the proverbia white cell count and its shift to the left Specific drug therapies are often no pertinent to this country—for example salbutamol is not part of their armamentarium for the treatment of asthma Otherwise most of their management strategie and guidelines I would have little to disagre about. The parent education chapter particularly contains useful material that w could all use. I was disappointed that th ingredients of the 'pudding' take up th first 182 pages, yet the results of implementing the system and the 'proof in it eating' is covered in just over nine pages What few data they give are impressive showing better antibiotic prescribing, improved clinical recording of information and a decrease in the number of investigations ordered.

The book would be better entitled 'Standard Setting and Performance in Genera Practice' but as the authors state on the las page that 'the system cannot be a substitut for inadequate resources' I cannot see th its aims could ever be achieved in th country, however laudable Don't wast your money!

E J Eastha
CONSULTANT PAEDIATRICIA
Royal Victoria Infirmar
Newcastle upon Tyn

Archives of Disease in Childhood, 1988, 63, 1421–1422

British Paediatric Association

Minutes of the Annual General Meeting

Minutes of the Annual General Meeting of the Association held on Wednesday 13 April, 1988. The President, Professor J O Forfar, took the chair.

1 WELCOME TO SECRETARY

The President welcomed to the meeting Mr Paul Dunn as the Secretary to the Association.

2 APOLOGIES

Apologies for absence were received from the following: Dr K S Anand; Dr Barbara Ansell; Dr Margaret Borzyskowski; Professor C Chantler; Professor J A Davis; Dr Katherine Elliott; Dr A W Ferguson; Dr Patricia Hamilton; Dr R W A Jones; Dr I A McKinlay; Dr B Qureshi; Dr A Robinson; Professor R J Robinson; Professor M L Rutter; Dr H C Spratt; Dr Rosemary Stephens; Dr Margaret Stoneman; Dr M K Strelling; Professor J H Walker.

3 MINUTES OF THE 1987 ANNUAL GENERAL MEETING

The minutes of the meeting held on 8 April 1987, which had been circulated to members in March in the Annual Report, were accepted and signed as a correct record.

4 ELECTION OF HONORARY OFFICERS

The meeting ratified Council's election of Dr J W Partridge to serve as Honorary Treasurer 1988–91 and Dr R F MacFaul to serve as Honorary Assistant Secretary 1988–90.

5 PRESIDENT'S REPORT

The President's Report had been circulated to members in March in the Annual Report and was APPROVED by the Annual General Meeting.

The meeting stood in memory of the members who had died since the last meeting: Dr Winifred Bartindale; Dr T A Brand; Dr Roma Chamberlain; Dr W Davies; Professor I Donald; Professor R Dubois; Dr R C Evans; Dr Rita Forrest; Dr M Friedman; Professor W F Gaisford; Professor J Hutchison; Dr Teresa Posmyk; Dr D M Ricks; Dr Marsha Simons; Dr Jean Thomas; Dr Vera Wilkinson.

Progress had been made on the integration of the child health services at the professional level; the administrative implications had yet to be implemented. The President referred to the need for the paediatric subspecialties to be recognised as part of paediatrics.

The Association had accepted *Achieving a Balance* which incorporated the recognition of paediatrics as an acute specialty and recommendations for a safety net.

In the context of an increasing willingness of the government to consult the Association on matters concerning paediatrics and child health, meetings had taken place with a Minister of Health and the Parliamentary Under Secretary of State for Health.

The President thanked the Secretary and the other members of the secretariat for their hard work and valuable contributions to the work of the Association.

6 ELECTION OF NEW MEMBERS

Professor S M S Ali Taha, Professor N R Butler, Professor A Clarke, Dr G Duncan, Professor J Lorber, Professor F Monckeberg, Professor M F Oliver, Mr G D Pinker, Sir Alan Reay, and Dr P Soysa had been proposed for Honorary Membership and there were nominations for 116 Ordinary Members, 27 Overseas Members, and 28 Associate Members. The meeting approved the nominations and the new members were duly elected.

7 TREASURER'S REPORT

The Treasurer presented the Accounts for the period 1 January to 31 December 1987. These had been circulated to members with the Annual Report and had subsequently been audited. There had been a surplus for the year and the Association's reserves had been increased, mainly by substantial profits from sales of the *Archives of Disease in Childhood* and a donation from the Royal College of Physicians of London towards the cost of moving to and establishing the new premises at 5 St Andrew's Place. Council had approved the funding out of reserves of a study of the workload in children's units and also of an updating of the Association's statistics on paediatric manpower.

British Paediatric Services Ltd had been established in August 1987 and registered for VAT to undertake trading activities on behalf of the BPA. Profits earned by the company, chiefly from the Annual Meeting Trade Exhibition, would be covenanted to the Association.

The BPA's financial status which had considerably strengthened in recent years provided a sound basis on which plans could be made for the future.

The Honorary Treasurer thanked Mr Michael Ray, the Association's financial adviser, and the secretariat for their work in preparing the accounts.

The Honorary Treasurer's verbal report and the circulated Accounts for 1987 were APPROVED.

Dr J W Partridge proposed a vote of thanks to the retiring Honorary Treasurer for his hard work during his period of office. The present satisfactory state of the Association's finances was a tribute to his able administration over the last five years.

8 MEMBERS' SUBSCRIPTIONS

The meeting agreed that the annual subscription rate for Ordinary Members should be increased to a point within the range £98 to £103 from 1 January 1989, with pro rata increases for lesser rates. The final figure would be submitted to Council for approval in June.

9 APPOINTMENT OF AUDITORS

The meeting appointed Messrs Arthur G Mead & Co as auditors for the financial year 1988–89

10 REPORT OF THE ACADEMIC BOARD

The Report of the Academic Board which had been circulated to members in March in the Annual Report was received

11 REPORTS FROM STANDING COMMITTEES, WORKING PARTIES, PAEDIATRIC SPECIALTY GROUPS, AND OUTSIDE BODIES

The meeting received reports which had been circulated in the Annual Report to members in March. The President thanked all those who had served and contributed to this significant part of the Association's work.

12 DIAMOND JUBILEE

On 2 February the establishment of the Association exactly 60 years previously was celebrated at a reception held in 5 St Andrew's Place. A poster demonstration on the theme 'Make Children a Priority Again' was mounted for a week in February in the House of Commons. The exhibition was opened by Lord Skelmersdale and was attended by Ministers of Health and other Members of Parliament.

A reception would be held in the House of Lords on 19 May. Arrangements were being made for Child Health Week in October; it was hoped that the many activities at local level during the week would further the work of caring for children in hospital and in the community. A thanksgiving service in Westminster Abbey on 12 October would be followed by a dinner in the evening at the Royal College of Physicians of London.

Publication of *Child Health in a Changing Society* was expected in May, to be followed later in the year with the publication of an updated history of the Association. The President thanked all those who had contributed to these works.

13 THE FUTURE REPRESENTATION OF PAEDIATRICS

The meeting received a paper describing progress since the referendum. The opinion of members of the Association was evenly divided between the two options: Joint Faculty or Independent College. A Subcommittee had been appointed by Council to examine these on the basis of the objectives unanimously agreed at the 1987 AGM. The committee had considered the need for unity among paediatricians, the question of standard setting and the status of Faculties. Council had approved the following proposal as a basis for uniting all paediatricians on an agreed policy: 'To implement the objectives agreed at the 1987 AGM, Council recommends that steps be taken to establish a College of Paediatricians interdependent with the three Royal Colleges of Physicians'. It was intended that, if the meeting approved the resolution, the Subcommittee would look at how it would be implemented and bring to Council a detailed proposal about the most appropriate structure for any future body representing paediatrics. The Royal Colleges of Physicians would then be approached for further discussions. A referendum of the members would follow. After full discussion the resolution was carried by overwhelming majority with only four dissenters.

14 VOTE OF THANKS TO THE RETIRING PRESIDENT

Dr C H Nourse paid tribute to the contribution of Professor J O Forfar to the work of Association during his term of office as President. The strength, enthusiasm, and vigour with which he had pursued the aims and policies of the BPA had significantly advanced their progress. His remarks were endorsed with acclaim.

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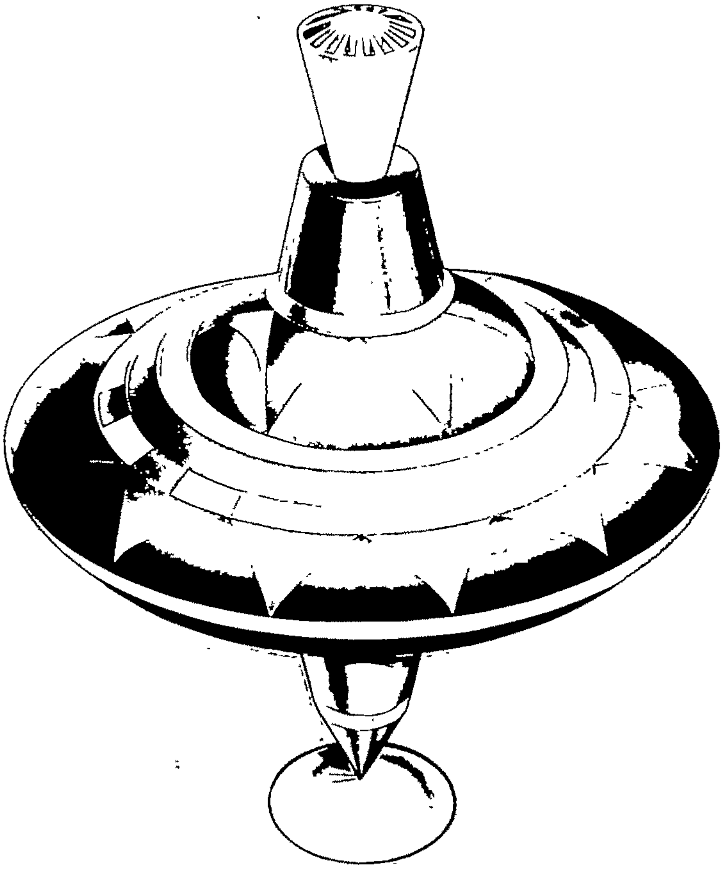

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Subscription information

Volume 147 (6 issues) will appear in 1988. Information about obtaining back volumes and microform editions available upon request

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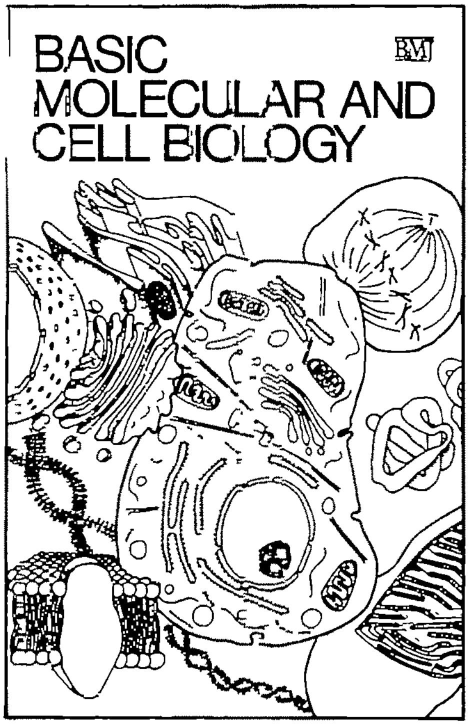

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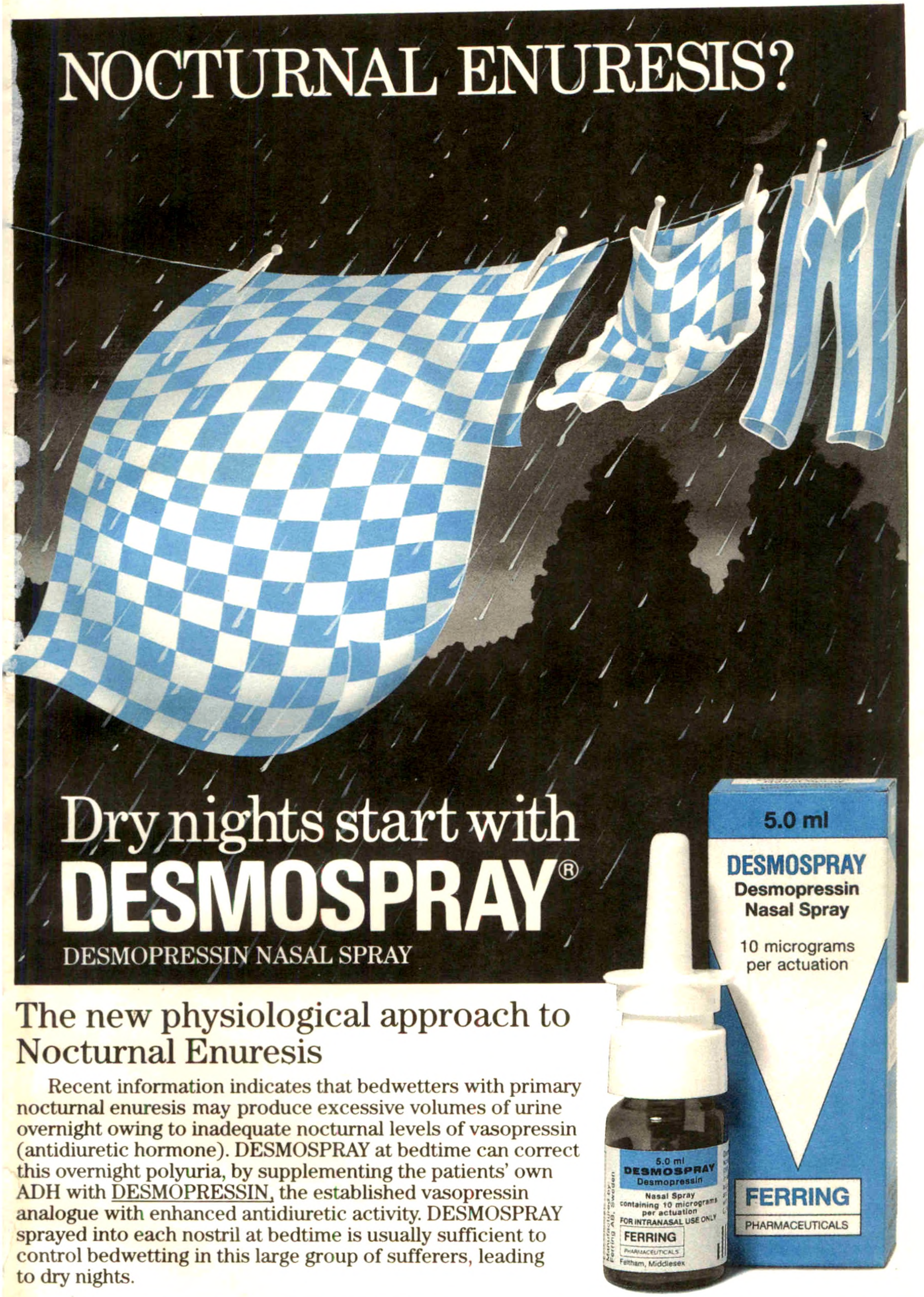

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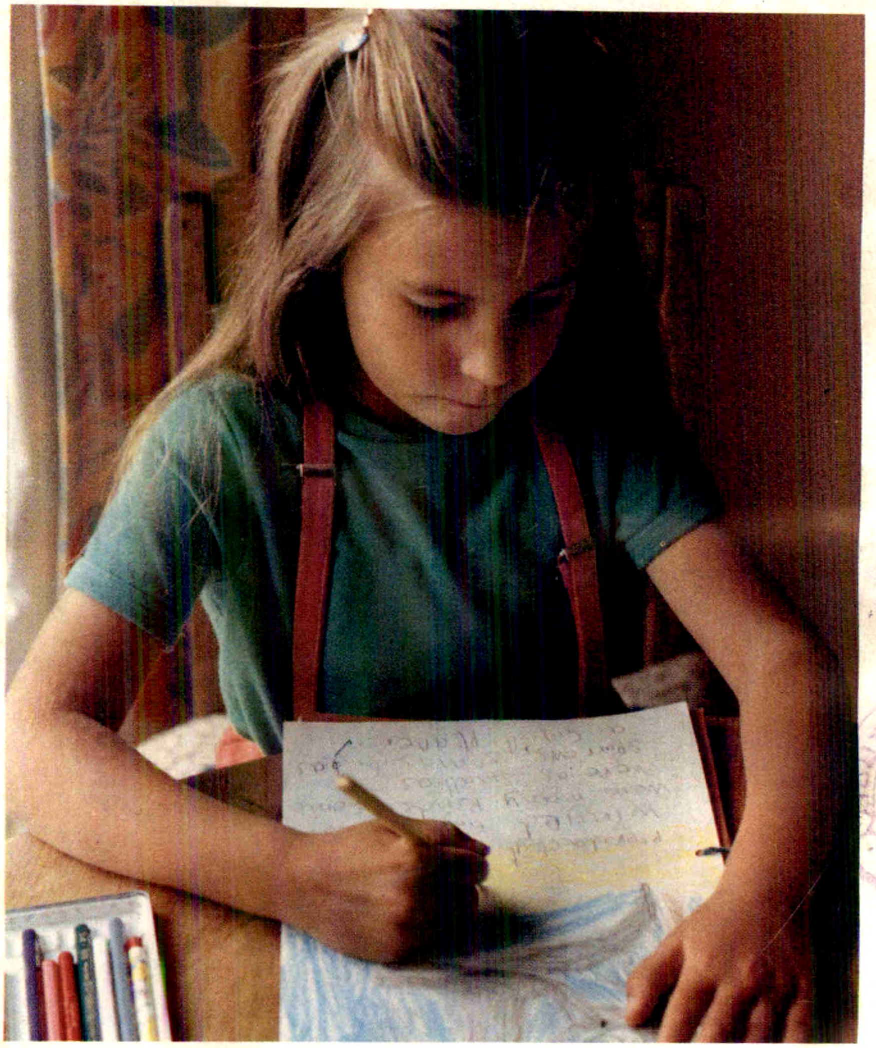

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